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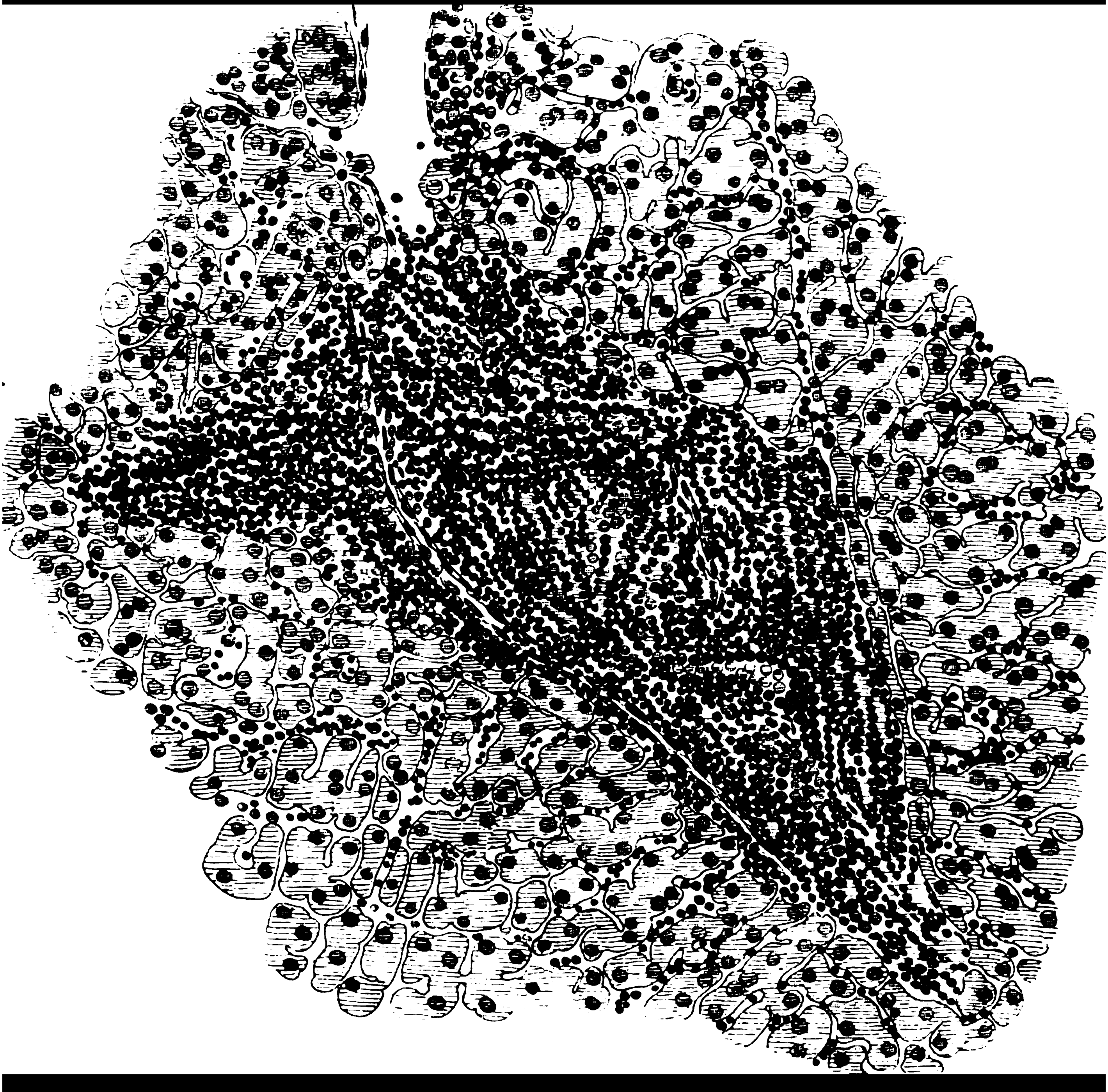

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STUDIES IN TYPHOID FEVER.

BY

WILLIAM OSLER, M. D., **GEORGE BLUMER, M. D.,**
SIMON FLEXNER, M. D., **WALTER REED, M. D.,**
AND
HAROLD C. PARSONS, M. D.

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THE MALARIAL FEVERS OF BALTIMORE.

AN ANALYSIS OF 616 CASES OF MALARIAL FEVER, WITH SPECIAL REFERENCE TO THE RELATIONS EXISTING BETWEEN DIFFERENT TYPES OF HAEMATOZOA AND DIFFERENT TYPES OF FEVER.

By WILLIAM SYDNEY THAYER, M. D., and JOHN HEWETSON, M. D.
Assistants in the Medical Clinic.

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I.—PRELIMINARY REMARKS.

During the five years between June 14th, 1889, and August 1st, 1894, 616 cases of malarial fever were treated in the wards and in the medical out-patient department of the Johns Hopkins Hospital. In a considerable number of cases occurring in the out-patient department, hasty or insufficient examinations of the blood failed to show the specific micro-organisms, while in other instances examination of the blood was omitted on account of lack of time. Most of these cases are classified in the hospital records as "malarial fever?"; they have not been included in our analysis. Excepting two or three instances where the patients entered the hospital during convalescence, the specific micro-organism was found in every case of malarial fever treated in the wards.

The writers of this article have observed practically all the cases here classified after October, 1890. In a number of those observed before this time careful notes or drawings were made, which enabled us to draw definite conclusions with regard to the type of the organism. In other cases, however, the entries upon the records were so vague that, while the charts might justify a more or less decided opinion as to the nature of the infection, we have not included them among those cases where the type was definitely differentiated.

As a result of our observations, we believe that we have been able to recognize certain distinct types of parasites which appear to be related in turn to certain almost equally characteristic types of fever. It is the principal object of this paper to determine by a careful analysis of all of our cases in how far our impressions may be justified, and to compare our results with those of the numerous recent observers in this and in other countries.

We have prefaced our analysis by an historical summary of the more important literature concerning the malarial parasite.

At the end of the article will be found a table of references arranged, as far as possible, in chronological order. This we believe to be a fairly complete list of the publications concerning malarial fever which have appeared since the recognition of its parasitic origin.

A great mass of literature from sources where the relation of the haematozoa to the disease is as yet unrecognized has been of necessity passed by.

The table also contains references to the works which have recently appeared on the haematozoa of birds, as well as to the more important articles on haematozoa in other animals.

II.—LITERATURE.

DEVELOPMENT OF OUR KNOWLEDGE CONCERNING THE MALARIAL ORGANISM: ITS MAIN MORPHOLOGICAL AND BIOLOGICAL CHARACTERISTICS.

Since the discovery by Lewis,(8) in 1879, of living parasites in the blood of rats, the pathogenic importance of haematozoa, both in man and in other warm-blooded animals, has claimed yearly more and more attention; and doubtless the most important discovery which has been made in this field is that of Laveran, who in 1880, was able to announce that he had found, in the blood of individuals suffering with malarial fever, living parasites which were, in his opinion, the probable cause of the disease.

The infectious origin of malarial fever has, as is well known, been suspected for many years; it is, however, quite beyond the scope of this article to enter into a discussion of the numerous and interesting theories which have existed in the past.

The presence of pigment in the blood was first noted by Meckel (1) in 1847. In an autopsy on the body of an insane woman who had suffered from malarial fever, he not only observed the presence of pigment in the blood, but pointed out in addition that the pigment was contained for the most part in round, ovoid or spindle-shaped protoplasmic masses which were doubtless the malarial parasites. He did not, however, recognize any connection between the pigment and the malarial process.

As long ago as 1848 Virchow (2) described and pictured, in the blood of an individual dead of malarial fever, pigmented bodies, many of which were probably phagocytes, while others, from the description and from the accurate drawings, were unquestionably examples of what were not to be recognized for thirty-two years as the pathogenic parasite. Hischl,(3) in 1850, recognized the connection between the presence of pigment and intermittent fever. Planer,(4) in 1854, noted the pigment in the circulating blood, and suggested its origin there as well as in the spleen. He believed that the pigment circulating in the blood arose during the fever, and that it was the cause of many of the symptoms.

The association of melanaemia and pigmented leucocytes with malarial fever, and the diagnostic importance of this condition was thus recognized in many quarters when Laveran in 1880 discovered the fact that the pigment was primarily contained in the body of a living parasite. Laveran,(14, 15, &c.) a French military surgeon, was at this time stationed at Constantine in Algeria. He had set for himself the task of studying carefully the malarial fevers. In November 1880, while examining the blood of a patient with malarial fever, he noted several of these pigmented bodies which possessed long, actively moving filaments which oscillated about among the surrounding corpuscles in so active a manner as to convince him that he was looking upon a living parasite. On the 24th of December, 1880,(16) in a report to the Société des Hôpitaux, Laveran presented the results of his studies in 44 cases of malarial fever, in 26 of which he had found elements which he believed to be parasitic. He described three forms of the organism:

(1). Crescentic or ovoid bodies, 8 to 9 μ in length by 3 μ in diameter; these were quite transparent and colorless, except for a collection of rounded pigment granules near the centre, or more rarely, collected toward one end of the body. Oftentimes the granules were arranged in the shape of a crown or wreath. At times the extremities of the crescentic bodies were connected by a pale, curved line. Change of shape, if there was any, was very slow and slight.

(2). Bodies which in repose were spherical, transparent, about 6 μ in diameter, containing a ring of rounded pigment granules of about equal size. In activity, however, these bodies were surrounded by from three to four fine filaments in active, worm-like motion. The length of these was three to four times that of a red corpuscle, possibly longer, while their ends were slightly swollen and clubbed. They arose at times all from one side of the body, while at others they took their origin from different parts of the periphery. The central body was at this time in extremely active motion, the pigment granules dancing about and changing their position, while the movements of the central body as a whole were like those of an amoeba. At times one of the filaments might be seen to separate from the body and move about free among the corpuscles.

(3). Bodies which were generally spherical, 8 to 10 μ in diameter or sometimes more, slightly granular and non-motile, without peripheral filaments. The pigment granules were generally arranged without regularity, and varied in number. The bodies might be seen to become gradually irregular in shape, while the pigment was usually non-motile. He believed that these were simply cadaveric forms of the former parasite. Furthermore he found generally in his preparations small, rounded, refractive, motile bodies and granulations of pigment of a fiery red or of a clear blue color.

These organisms he found only in malarial fever. They disappeared on treatment with quinine. He concludes that "there exist in the blood of patients with malarial fever, parasitic elements which have heretofore been confounded with melaniferous leucocytes; the presence of these parasites in the blood is probably the principal cause of the manifestations of paludism." Concerning the nature of these bodies Laveran raised the question as to whether they were amoebae or whether possibly bodies 1 and 2 were produced by an agglomeration in a species of cyst formed, perhaps, at the expense of normal elements of the blood, of parasites which, in their full development, were represented by the motile filaments which might, at times, become detached and lead an independent life. To this latter view he inclined.

This preliminary report, which was received with general scepticism, was followed by a number of other notes, in which Laveran defended his former statements, while in 1881 a small monograph (25) appeared, setting forth his observations at greater length. In this monograph the name "Oscillaria malariae" was suggested as a proper one for his newly-discovered parasite. In the same year, before the Academy of Sciences, (23) Laveran added still another form of the parasite to those already described:

These bodies were spherical, transparent elements, containing motile or non-motile pigment granules; they were, however, much smaller than the other forms which had been described, the diameter varying from one-sixth that of a red blood corpuscle upwards to nearly an equal size. The smallest had but one or two fine pigment granules, while again they might be nearly the size of a leucocyte, and contain numerous actively motile granulations. "These bodies, sometimes isolated, sometimes together, as many as four, sometimes free in the blood, sometimes attached (accolés) to the red corpuscles or leucocytes, seem to represent simply one of the phases of development of the parasitic bodies above described." He still adhered to the view that these pigmented bodies were cysts containing the motile filaments, which in the free stage represented the organism at its stage of most perfect development. He also stated his belief that "it is because it kills these parasites that quinine causes the disappearance of the manifestations of paludism."

The first observer to confirm these observations was Richard,(26) who pursued his studies in 1882 at Phillippeville, in Algeria. He describes carefully the development of the body, stating that in the beginning it is represented by a small, perfectly clear spot in the otherwise normal corpuscle ("toute petite tache claire"). This, growing, develops pigment, while the corpuscle containing the organism becomes decolorized, and finally is reduced to a mere shell, the body developing within it like a weevil in a lentil. At times the organism may escape from this shell which may be seen as a pale rim upon one side. He describes vividly the motile filaments, the crescents, and the melaniferous leucocytes, enlarging thus the observations of Laveran by describing a little more definitely the earliest stages of the body (non-pigmented forms), and differing from him in considering the bodies intra-corpuscular instead of being attached merely to the body of the red corpuscle. Later,(33) however, Richard abandoned the idea of the intra-corpuscular condition of the parasites, accepting Laveran's theory that they were attached to the surface of the corpuscles. He believes with Laveran that the motile filaments represent the organism at its most perfect stage of development. He agrees also with Laveran in the statement that the organisms are present in greater numbers on the days of the paroxysms. They develop rapidly, their number increasing till the beginning of the paroxysm; "they produce the fever, the fever kills the parasite, and falls in its turn." During apyrexia the parasites grow again, until finally another paroxysm is produced. The continuous fevers, where quinine fails to act, Richard believes to be non-malarial.

At the time of these discoveries by Laveran and Richard, the eyes of the world were directed much more toward the work which was then being carried on in Italy by Klebs, Tomassi Crudeli, and other observers,(9, 12, 13, 17, 21, 27, 28, 32, &c.) who believed that they had isolated a bacillus which had a direct etiological relation to malarial fever, and the work of the French observers was received with great scepticism, nowhere more so than in Italy. There, Marchiafava and Celli,(34, 35, 36) who, among others, were believers in the bacterial origin of malarial fever, studied, by means of dried and stained specimens, the changes which occurred in the red blood discs in paludism. In many of the red corpuscles they found small round bodies resembling micrococci, which took up methylene blue, as well as slightly larger ring-shaped forms; further they found larger areas containing dark pigment granules, until finally whole corpuscles were sometimes taken up by large, palely staining pigmented bodies. They suspected that the small spots first mentioned might in some instances be parasitic (micrococci) in nature, while the larger pigmented areas they believed to be degenerative changes in the red discs, changes which had been brought about possibly by the presence of parasites. The plates show that most of these stained bodies were unquestionably malarial parasites.[*] They noted that the pigment was formed in the circulating blood at the expense of the red blood corpuscles. Later,(36) in a more extensive article, they followed carefully the development of pigment, and described again these so-called degenerative changes in the corpuscles. They referred to the changes which occur in the red corpuscles when exposed in tubes to high temperatures, 42° to 48° C. (the development of motile filaments), and stated without further discussion that these represented the filaments observed by Laveran and Richard. The crescents, they said, were due simply to decolorization of the periphery of the corpuscle while the rest retained its color. It was not until 1885 that Marchiafava and Celli (41, 45) recognized the fact that they had been dealing with a parasite and not alone with degenerative changes. They had then seen the flagellate bodies of Laveran in four cases out of forty-two; they had also seen bodies similar to these with an extremely active, wave-like movement of the peri-

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[*] A number of the smaller dots, those resembling micrococci, were probably similar to those areas found in all anaemias, and described by Ehrlich as degenerative changes.

phery. They described also bodies where the pigment had collected in the middle, the substance of the parasite showing evidences of differentiation into a number of smaller bodies, while in others the pigment was surrounded by a collection of distinct segments into which the organism had divided. They laid particular stress upon the smaller forms of the parasite, and stated that it was then certain that they did not belong to the class of schizomycetes. They inoculated healthy individuals in five cases with the blood of malarial patients with fairly good results, in as much as in all instances, after several inoculations, symptoms of malarial fever with the presence of parasites in the blood were produced in the individuals upon whom the inoculation was practised. Later (45) in the same year they described with great care and accuracy the characteristics of the small hyaline forms. These they described as showing an outer, thicker, more refractive zone, and an inner, less refractive part, which appears sometimes finely granular. The organisms are actively amoeboid, the pseudopodia extending from the outer zone. This outer zone alone is colored by staining reagents, the central part being so thin that the red corpuscle shines through; at times it has the appearance of a clear or slightly colored nucleus. In some instances no pigmented forms whatever were seen, though in several of these cases pigmented leucocytes were found. Among these cases were some of the most severe and pernicious forms. They believed that these parasites were contained within the red corpuscles in opposition to the views of Laveran and Richard, who, it will be remembered, considered them attached to the surface. They described more extensively the segmenting bodies, and suggested that these might represent a process of reproduction, as they had noticed, in one instance, their occurrence during the paroxysm simultaneously with the appearance of new hyaline bodies in other corpuscles. In this early communication they described, in the organs of certain pernicious cases, the appearance of these segmenting forms in small parasites which were quite free from pigment. They claimed for themselves the honor of having first described the small non-pigmented forms, which they considered the most important elements, asserting that the bodies described by Laveran and Richard were vacuoles or other changes in the red corpuscles. They proposed for these small bodies the term "Plasmodia." Thus it will be seen that Marchiafava and Celli have the honor of having first called attention to the extreme amoeboid activity of these small forms, and also that they were the first to describe and suggest the importance of the segmenting bodies. It can, however, hardly be doubted that Richard's description of the hyaline forms was based upon observations of these same bodies, and not upon vacuoles as Marchiafava and Celli assume, and, while the honor of first describing and of hinting at what has later been shown to be the true significance of the segmenting forms, belongs unquestionably to them, there is, at the same time, no doubt that these bodies had been observed by Laveran some years before. Laveran(60) has indeed published a very clear and accurate plate of a segmenting form occurring during the paroxysm in a case of quartan fever; the sketch was made in 1881. Marchiafava and Celli further vigorously assailed Laveran's ideas concerning the nature of the organisms, denying that they are cystic in character, and denying also the double contour which Laveran and Richard describe in the crescents and ovoid bodies.

Following these articles of Marchiafava and Celli, the literature of malarial fever shows an almost continuous series of articles confirmatory of the discoveries of Laveran. No observers, indeed, of importance who have had opportunities for proper study of malarial blood, have failed to confirm his observations. Among the first of these observers were Councilman and Abbott,(40) who in 1885, in the study of the organs from two cases of comatose pernicious malaria, described pigment-containing bodies in and outside of the red corpuscles, particularly in the capillaries of the brain, and also in the liver and spleen, as well as numerous pigmented phagocytes. They had not been able to find these bodies in the fresh blood, but they remarked their similarity to the parasites described by Laveran. They had not been able to find the bacilli of Tomassi Crudeli.

In 1885, then, our knowledge of the malarial parasite, based upon the observations of Laveran, Richard, Marchiafava and Celli, Councilman and Abbott, may be summed up as follows. There had been observed small, hyaline, amoeboid, intra-cellular parasites, which grew gradually, developing within themselves fine, actively motile pigment granules; these bodies eventually generally filled up the entire corpuscle, decolorizing and perhaps destroying it. Having reached this full-grown stage, the organisms were in some instances seen to show a concentration of the pigment in the centre of the body with the development of a radial striation and the formation of segments, while in other instances, they appeared to give rise to the motile filaments first described by Laveran. Sometimes the small, intra-cellular bodies appeared to develop into ovoid or crescentic forms with the pigment granules in the middle. The crescents had apparently the power to change again into the ovoid, and then into a round shape, from which, commonly, the flagellate bodies of Laveran were seen to develop. The significance of these different forms was a much disputed point, Laveran believing the most perfect forms of the organism to be the free flagella which develop in the interior of small cysts which were represented by the earlier forms, while Marchiafava and Celli were inclined to believe the parasite to be more like an amoeba, denying entirely its cystic nature. Concerning the significance of the segmenting bodies, Laveran was, at first, apparently inclined to believe that these were rather degenerative forms, while Marchiafava and Celli suggested, distinctly, their reproductive nature. The observations of Laveran showed that the crescentic forms were found more particularly in the patients who had been suffering from chronic and severe malarial fever or relapses.

In the year 1885 a new era in the study of the malarial organisms was introduced with the publication of the researches of Golgi,(49) of Pavia. And from this time, as Barbacci (239) has pointed out in his admirable review of the subject, we must recognize two main schools, with essentially different views concerning the nature of the malarial parasite.

The first party is represented by Laveran and his followers who believe that the malarial parasite is a single polymorphous organism; that there is no constant relation between the different forms in which it appears and the various types of fever.

The second party, at the head of which stands Golgi, believes that, corresponding to and associated with the main types of malarial fever, one may distinguish different types of the malarial parasite, or, possibly, different parasites.

The views of the first party may be summed up in part in Laveran's (277) own words: "This parasite is to be seen in a considerable variety of forms, which one can, however, resolve into the four following types: (1) spherical bodies; (2) flagella; (3) crescentic bodies; (4) segmenting bodies or rosette forms."

(1). He describes the different stages of development of these bodies from the small amoeboid hyaline forms onward. The movements of the pigment granules he believes to be communicated by undulations of the protoplasm. The bodies themselves are sometimes free, sometimes attached to the red blood corpuscles; sometimes several may be attached at one time to a single corpuscle. The development of the parasite occurs at the expense of the red blood corpuscle which becomes decolorized and sometimes disappears altogether. Sometimes one large body may be seen to break up into a number of smaller ones. At times also small sarcodic buds may be seen to form at the periphery of a larger body. These he apparently considers to be reproductive processes. He describes also the gradual deformation and death of some of the large pigmented forms.

(2). The flagella, he asserts, may be seen immediately after the specimen has been prepared, especially if the weather be warm, though ordinarily it is easier to find them in from fifteen to twenty minutes after the beginning of the examination.

At the further extremity of the flagellum one may often see a pyriform swelling, and similar ovoid enlargements may, at times, be made out at different points in the course of the filament. At times a small particle of pigment may be seen to pass into the flagellum as if through a central canal.

After the breaking off of the flagella, which doubtless pursue a separate existence, the body of the parasite is left deformed and motionless—a cadaver.

(3). After describing the crescents as before, he notes that the fine line, which often connects the two horns, represents, doubtless, the remains of the red blood corpuscle at the expense of which the crescent has developed.

(4). The segmenting bodies he describes and pictures as has been noted before. The plates illustrating the segmenting bodies, it is interesting to note, were from drawings made in 1881, which had not been published at that time.

Concerning the development of the parasite he says: "The small hyaline bodies not yet pigmented, which form the little clear spots on the red corpuscles, represent, probably embryonic forms of the parasite; little by little these bodies increase in size till finally their volume equals or even exceeds by a little that of the red corpuscles;

at the same time the number of pigment granules increases; these elements, which possess the power of amoeboid movement, live in a free state in the serum of the blood, or adhere to the red corpuscles at the expense of which they derive their nourishment and their pigment; the flagella develop in the interior of the spherical bodies and at a given moment become free."

The crescents (280) he believes to be encysted forms which develop from the spherical bodies. These forms show a much greater resistance to quinine than the spherical bodies; they may be seen to change into round, ovoid and flagellate forms.

He writes as follows in his last work: (377) "I do not believe that there exists a constant relation between the forms under which the haematozoa appear in the blood and the clinical manifestations of paludism; one can only say that certain forms of the parasite are more often seen in certain cases, the crescents, for example, in relapses and in malarial cachexia, as I have demonstrated long ago" . . . "The differences which one makes out in the evolution of the haematozoa of paludism are not sufficient to authorize one in admitting the existence of several distinct varieties of parasites."

The views of the other school must be entered into at greater length; they date, as has been said, from the researches of Golgi in 1885.

With the appearance of the articles of Golgi on the organism of quartan fever begins, as we have already said, a new era in the history of the haematozoa of malaria.

In the study of twenty-two cases of quartan fever Golgi (40) followed with singular care and accuracy the development and life history of the parasite, determining for the first time the close relations which exist between the development of the organism and the clinical symptoms. Marchiafava and Celli had already mentioned that they had found segmenting bodies during the paroxysm, but Golgi was the first to point out that each paroxysm is always associated with the segmentation of a group of malarial organisms, in other words, that the beginning of every malarial paroxysm corresponds to the ripening of a generation of parasites. He further determined that, generally speaking, the severity of the attack is dependent upon the number of parasites present in the blood.

The parasite of quartan fever, upon the study of which these conclusions were based, requires seventy-two hours for its complete development. In their earliest stage the parasites are represented by small, amoeboid, hyaline, intra-corpuscular bodies. Early in the first day of apyrexia one finds, in the red corpuscles, unpigmented forms which are from about one-sixth to one-fifth the diameter of the corpuscle itself; these move slowly, changing their outline. The blood corpuscles in which they lie are of normal size and appearance. These bodies grow gradually larger without changing their general appearance, and develop rather coarse, dark brown pigment granules. Sometimes they may be seen free in the plasma, but this occurs rarely. The movement of the granules, as well as the amoeboid movement of the organism, whether it be intra- or extra-cellular, is always rather slow. Early in the day of the paroxysm the process of reproduction begins, the organisms having by this time so far increased in size as to entirely fill the red corpuscle, of which there is often only a slight peripheral rim remaining. Often, indeed, there is apparently no trace of the corpuscle left, so that one sees free bodies of a colorless substance with irregularly distributed pigment. Gradually the pigment becomes concentrated toward the middle of the body, until finally it forms a sharply defined clump in the centre. At this time one begins to see the appearance of a slight radial striation in the hyaline substance of the organism, the striae becoming more distinct until finally the central pigment clump is surrounded by eight to ten round or pear-shaped bodies, each with a small refractive central point, as regularly arranged as the leaves of a marguerite, the so-called rosette or marguerite forms of Golgi. Soon these bodies become more distinctly separated from one another and from the central mass, until the central pigment clump may be seen to be surrounded by four, to six, to eight, to twelve ovoid or round, clear, hyaline bodies, each with a small refractive central point. This segmentation begins eight to ten hours before the paroxysm, and continues during its first hours, while at the same time fresh hyaline bodies begin to appear in the red corpuscles. The resemblance between these segments and the fresh hyaline bodies is striking, although the actual entry of the newly formed segment into the corpuscle has never been observed. Based upon these observations Golgi founded the following laws: Each febrile paroxysm is closely connected with the cycle of development of a generation of parasites: the beginning of each paroxysm corresponds to the maturity of a generation of parasites: the severity of the paroxysm is, in general, proportional to the number of the parasites which are found in the blood. Some cases of quotidian fever which Golgi observed were due to infection with three groups or generations of quartan organisms, the groups maturing on successive days, causing thus a daily paroxysm, while in other instances, where chills were observed on two successive days with an intermission on the third, he was able to trace infection with two groups of parasites.

This description of the cycle of existence of the quartan organism was confirmed a few months later by Osler(55) in Philadelphia, and has since then been accepted by practically all who have had opportunity to study quartan fever.

Antolisei,(126) in a systematic study of the parasite of quartan fever, added little to Golgi's observations. He laid more stress upon the beginning of segmentation before the actual onset of the fever. While Golgi believed the paroxysm to be due to the invasion of the red corpuscles by the new generation of parasites, Antolisei held that the chill depended rather upon the act of segmentation than upon the actual invasion of the corpuscles. For, by administering quinine in sufficient quantity shortly before an expected paroxysm, the invasion of the red corpuscles by a fresh generation of parasites may be completely prevented, while it is quite impossible to prevent the impending segmentation or the paroxysm. He believed the segmenting parasite to be surrounded by a membrane consisting of the more resistant outer layer of the red corpuscle in which it has developed; this membrane is broken through with the setting free of the segments.

These observations concerning the quartan organism were followed in 1886(80) and 1889(94) by further careful studies of the parasite of tertian fever. This parasite begins its cycle, as does that of quartan fever, as a small, hyaline, unpigmented body; this increases in size and develops pigment during forty-eight hours, at the end of which time it reaches its complete development; it then undergoes segmentation just before and in association with the paroxysm, at which time the appearance of a new generation of organisms in the red corpuscles is to be observed. Golgi noted, however, distinct differences between the tertian and the quartan organisms. In the first place, the amoeboid movements of the young tertian parasite are much more active; the granules are smaller and of a somewhat different color (a lighter, more reddish brown); the outlines of the body in general, which are quite clear and sharply defined in the quartan parasite, are, in the tertian, very indistinct. The dancing of the granules is also much more active in the tertian organism. With the growth of the quartan parasite the red corpuscle remains about its normal size, or, indeed, tends to shrink about the body, while the decolorization does not occur until later on, so that the organism may have reached almost its complete development without any particular change in the color of the red disc. In tertian infections, however, the corpuscle begins to be decolorized early in the development of the parasite, and instead of tending to shrink about the body, it becomes considerably expanded and swollen, so that at the time of complete development of the parasite it may be very much larger than its normal neighbor. The full grown tertian organism is then somewhat larger than the quartan parasite.

In segmentation also there are material differences between the organism of tertian and that of quartan fever. Golgi describes two distinct varieties:

(1). The pigment gathers in the centre of the body, while a certain differentiation may be made out between the peripheral clear protoplasm and the central part with the pigment; indications of a radial striation begin to appear in the peripheral clear protoplasm, which eventually becomes divided into from fifteen to twenty small hyaline segments. The differences between this mode of segmentation and that of the parasite of quartan fever are, according to Golgi:

(*a*). The greater number of segments, from fifteen to twenty.

(*b*). The difference in the size of the individual segments which are smaller in the tertian parasite.

(*c*). The absence of the central refractive spot in the tertian parasite.

(*d*). The fact that the pigment which gathers in the centre appears here to be contained in a protoplasmic body.

These pigmented bodies Golgi believes to be for the most part, taken up by phagocytic leucocytes, though he does not feel sure that some of them may not remain in function and produce other bodies.

(2). This variety of segmentation differs from the first in that after the pigment has collected into a small clump, the whole mass of the protoplasm becomes divided into small round bodies, which do not have the regular daisy-like arrangement of the segments in the first variety, but form simply an irregular clump of small spheres about a central free pigment mass.

Golgi suggests a third variety of segmentation, which is probably rather a degenerative process. Here, in the free pigmented body, which has entirely destroyed the red corpuscle, the pigment collects in a point nearer the periphery, leaving a part of the corpuscle entirely clear and transparent. Within this clear area one and sometimes two small spheres develop, which resemble the true spores.

With the tertian as with the quartan organisms, Golgi observed that quotidian fever depended on infection with more than one group of the parasite; he had observed no organism whose cycle of existence lasted but twenty-four hours. This description of Golgi's of the cycle of the parasite of tertian fever has been in the main confirmed by later observers, though it has met with criticism in some respects and with certain additions.

Antolisei,(129) in 1890, in a careful study of the parasite of tertian fever, agrees with Golgi in the main points. He has, however, met with Golgi's second form of segmentation only, while he asserts that the third variety of segmentation is a degenerative process. He describes this process of vacuolization at length. When the pigmented body has wholly destroyed the red corpuscle, and is free in the blood current, one sees, at a certain time, the development, toward the periphery of the body, of a spherical area, into which the pigment granules which are in very active motion, never enter. Within this area one may see a white, sharply outlined sphere, about which there is very often a vacuole which has a semi-circular appearance because the sphere does not lie in the middle but presses to one side. Later there develop elsewhere in the protoplasm of the organism numerous smaller spherules of varying sizes. Between these lie the pigment granules which become motionless, while in the remaining protoplasm the activity of the movements seems to increase. Gradually more spherules appear, of varying size, often becoming steadily smaller, so that finally the whole body is represented by a collection of minute spherules with sharp outlines, between which lies motionless pigment; about them is an outer shell, which possibly represents the outer more resistant layer of the red blood corpuscle. In the meantime there generally arises a sort of hernia through the outer more resistant layer, which may take various forms; inside of this new spherules develop. This process of vacuolization Antolisei considers to be degenerative in nature, as does he also that of flagellation, which is seen to occur in large bodies exactly similar to those which undergo vacuolization. Furthermore, Antolisei believes that true segmenting bodies are rarely met with in the circulating blood. He asserts that these are not larger than a red blood corpuscle, whereas those forms which one often considers to be full grown tertian parasites are frequently considerably larger. He believes that the majority of these large forms which appear in the circulating blood are over-grown organisms which are no longer capable of reproduction; they undergo only degenerative processes, vacuolization, fragmentation, and flagellation. Those pigmented forms which are capable of producing true healthy spores remain in the internal organs and are not to be found in the peripheral circulation; they never grow as large as these large free forms.

Bastianelli and Bignami (152) have further studied tertian fever, comparing the blood taken from the finger with that from the spleen; they find that while during apyrexia there is no great difference between the character of the blood from these different parts of the circulation, at the beginning of the paroxysm a marked difference is noticeable. At this time the full grown segmenting bodies with their pigment clumps and new spores are rapidly accumulated in the spleen. These forms reach the spleen, they believe, just as do any foreign bodies which enter the blood current. This does not take place while the parasite is endo-globular, or so long as the red blood corpuscles are not gravely altered in their essential characteristics. They suggest that if this same distribution is not observed in quartan fever, it is probably because the red blood corpuscles are less deeply altered by the quartan parasite than they are by the tertian. They believe, as does Antolisei, that Golgi's possible third form of segmentation is a degenerative process. They found these bodies much more frequently in the blood of the spleen than in the blood of the finger, particularly toward the beginning of the febrile paroxysm. They also note that in the irregular quotidian fevers and in anticipating tertians, they find, always in the spleen, and sometimes in the finger, small segmenting forms with five to ten small spores which are collected about possibly but a single pigment granule, and contained in red blood corpuscles which are not so swollen as is usually the case in tertian fever; sometimes these forms may be free. They suggest, therefore, that in these cases the cycle of development of the parasite may be accomplished in a shorter time than under normal conditions. The large, free, pigmented bodies which may be observed to become fragmented, vacuolated, or to show flagella, they believe to be degenerate forms. They suggest that spontaneous recovery may be associated with the frequency of these forms in the blood. The accuracy in the main of these descriptions of the tertian and quartan parasites has been confirmed in almost all malarial districts; by Grassi and Feletti (206) in Sicily, by Canalis,(104) Patella,(141) Marchiafava and Celli,(144) Terni and Giardina (145) in Italy, by Mannaberg (291) in Austria, by Kamen (242, 243) in Germany, by Sacharow,(153) Titow,(177) Romanowsky,(210) and Korolko,(226) in Russia, by Remouchamps (321) in Holland, and by Dock,(240) one of the authors,(327) and Koplik (305) in the United States.

The student of the literature can, however, hardly fail to notice the difference between these large pigmented bodies of tertian and quartan fever, and the small hyaline bodies—the "plasmodia"—to which Marchiafava and Celli ascribed so much importance, forms which have a likeness only to the very earliest stages in the cycle of existence of the parasites just described. It will also be noticed that the crescentic bodies which played so important a part in Laveran's first descriptions of the parasite, do not occur in the cycle of development of the organism of either tertian or quartan fever. And later observations have tended strongly to show that these organisms are associated with a different type of fever, a form of fever which is seen only in the more malarious districts, which is rare in Pavia where Golgi studied, but common in Rome and Algiers where Marchiafava and Celli, and Laveran made their observations.

Golgi,(49) in his first note on the quartan organism, mentions that in one case with irregular fever he found crescents and ovoid bodies in the blood, and he suggests that these forms may have a special cycle of existence differing from that of the organisms already described.

One of the first observers to call attention sharply to the fact that the more irregular and continuous fevers were associated with a clearly different type of organism was Councilman.(87) In 1887 he speaks as follows: "The character of these bodies" (the malarial parasite) "varies in different forms of the disease. Although they seem in rare cases to run into one another, still, in general, we can say that where the plasmodia inside the red corpuscles are seen, the patient has intermittent fever, and where the crescentic and elongated masses are found he has either some form of remittent fever or malarial cachexia." At the conclusion of this paper he states that from the examination of the blood we are "not only enabled to diagnosticate the disease as such, but in most cases the particular form."

In 1889 Marchiafava and Celli (100) and Pietro Canalis (104) published almost simultaneously more elaborate descriptions of the type of organisms associated with the "aestivo-autumnal" fevers observed in Rome. The preliminary note by Marchiafava and Celli appeared before that of Canalis, the article of Canalis before that of Marchiafava and Celli.

Canalis gives a careful description of the organisms associated with this type of fever. He refers to the organism as the "semi-lunar variety." He traces the life-history and cycle of development with considerable care, dividing it into two phases: (1) a rapid cycle, and (2) a slower cycle associated with the development of crescentic bodies. He finds that Golgi's rule applies here just as in the more regular intermittent fevers; that each paroxysm corresponds to the maturation of a generation of parasites.

(1). The rapid cycle is difficult to follow in that the blood usually contains several generations of parasites in different stages of development, which are associated with attacks following one another at varying intervals. He believes, however, that the cycle is generally of not less than two days' duration, though he has seen it as short as twenty-four hours. In the first three or four hours of the attack, one finds small hyaline amoeboid intracorpuscular bodies of about one-sixth the diameter of a red blood corpuscle. These bodies show a clear annular peripheral ectoplasm and a more shaded central endoplasm, which, from its shape and situation, resembles a nucleus. Sometimes, instead of one darker central point, one may see two or even four. When the body is in repose the ectoplasm is sometimes quite refractive. Often the blood corpuscles which contain them are shrunken and misshapen. Sometimes one sees free bodies in the plasma. The parasites gradually grow, and the amoeboid movements become more active, while in the peripheral, ring-like, often somewhat refractive zone, one notices fine granules of a dark red or black pigment. The appearance of pigment begins sooner or later, depending probably upon the length of the cycle of development. Gradually the parasite increases in size while the pigment granules accumulate. At the end of the cycle there are usually but very few minute granules of pigment, rarely more than six or seven. These stages of development occupy the greater part of the cycle, while the later stages are more rapid in their course, and examples are much more rarely seen in the peripheral blood, the process taking place probably in the internal organs. The parasite increases in size and loses its amoeboid movement while the pigment granules collect in a group or in a small block at the centre of the parasite; sometimes they may be placed eccentrically. The organism has a more hyaline appearance, and the distinction between the ectoplasm and endoplasm is no more to be made out. The blood corpuscle in which the parasite lies loses its color which it had retained fairly well before. An indication of radial striation now appears in the protoplasm of the parasite which eventually breaks into from six to ten round or slightly ovoid segments which surround a group of pigment granules or a very small block. These segmenting forms are considerably smaller than those of tertian or quartan fever. By this time the substance of the red blood corpuscle may have wholly disappeared, or the wholly decolorized body may form a pale ring about the parasite or at one side of it. A striking difference between these forms and those of tertian and quartan fever is the small quantity of pigment in the last stages of development. Canalis, however, has never observed segmenting forms without pigment. The segmenting bodies are but rarely seen in the peripheral circulation, though, at the time of segmentation, one may often see the small pigment blocks which have been derived from them, either free or in phagocytes.

(2). The second cycle, that associated with the development of the crescentic bodies, occurs, sometimes, in association with the more rapid cycle, but, at other times, only after this more rapid course of development has been checked by the administration of quinine. He has never observed crescents at the beginning of the process; in one instance only, did they occur before the fifteenth day. He traces the gradual development of the crescents inside of the red corpuscles from the small amoeboid forms; these assume a long elliptical shape, with the pigment collected in the middle, and gradually take on a crescentic form, decolorize the corpuscle, and finally become free in the blood, showing a double outline which appears to be the evidence of a surrounding membrane. These crescents in turn change into long elliptical, ovoid, and finally into round forms, though the ovoid forms would appear to arise in some instances directly within the corpuscles, without having passed through the crescentic stage. While, in the ovoid and crescentic forms, the pigment is motionless in a clump or in a ring at the centre of the body, in the round forms it is often in active movement, and commonly arranged in the shape of a ring. The ovoid and round bodies show sometimes a double outline, sometimes not. Sometimes the crescents may change into round bodies before the red corpuscle is entirely destroyed. When the crescents have reached this stage sporulation may occur. These bodies, usually round or ovoid, have sometimes a double outline, and contain eight or ten small spherules. The pigment is sometimes in a solid clump in the middle, though more commonly arranged in the shape of a ring in the middle or at one pole. Sometimes the pigment is free, sometimes retained in a mass of hyaline protoplasm which may be extruded from the body. The fresh segments are round or slightly ovoid with an opaque central area and a clearer outer layer which suggests a double outline. The association of these bodies with the paroxysm and with the appearance of fresh hyaline forms in the red corpuscles, convinces him that this is a true sporulation.

The process of sporulation must be, according to Canalis, sharply distinguished from certain degenerative processes which one sometimes sees. "In this degenerative process" he says, "one meets with bodies which have lost their yellowish or ashy color and have become clearer, sometimes refractive, with a double contour much more marked than that of the ordinary parasite, while their substance is transformed into a mass of round or irregular bodies of various sizes, and with a single contour. If one continues the microscopical examination of one of these parasites during the course of several minutes, he may sometimes see that two or three of these spherules become united into a single body, forming, thus, irregular masses, which, continuing the process of fusion, give, finally, to the parasite an homogeneous aspect without traces of spherules.

"The pigment is sometimes arranged as a central crown, sometimes scattered irregularly at an extremity or at one side of the body. The points which distinguish this process from that of sporulation are: the refractiveness of the degenerating body; the inequality in size of the spherules; the absence in these spherules of a more opaque central area; their fusion into irregular bodies and finally into an amorphous mass." These forms may also be seen in complete apyrexia, without being followed by a paroxysm or by the appearance of fresh hyaline bodies.

The flagellate bodies are often observed here, though they cannot be proven to be a constant phase. They arise, always, from the round forms which do not show a double contour. They appear, generally, several hours before the beginning of the attack, sometimes during apyrexia at a distance from the attack. "They represent, assuredly, one of the last stages in the development of the parasite, for I have never seen them appear in the blood before the formation of the round bodies." The length of this cycle varies in different cases. The period from the beginning of the amoeboid stage to the appearance of the crescents lasts, probably, not less than three or four days; after the appearance of the crescents the round bodies may appear upon the following day, or later. Associated with this type of organism occur the more irregular and continued fevers, the pernicious fevers, as well as many cases of malarial cachexia and fever with long intervals.

Marchiafava and Celli (100) state that where Golgi was dealing with fevers which pursue a regular cyclical course, are never pernicious, and yield, often without, and always with quinine, these cases of "aestivo-autumnal" Roman fever show, usually, an acyclical course; the attacks occur generally daily, following one another at intervals of twenty-four or thirty-six hours; the paroxysms themselves are often of long duration, so that one may be engrafted upon another without the temperature ever reaching the normal point. The chill is often lacking, the patient complaining only of symptoms of continued fever. These cases often show a pernicious character; they rarely heal spontaneously, show frequent relapses, and are associated often with grave anaemia. Some of the most pernicious cases may show no rise in temperature. The examination of the blood at the acme of the fever, and, also, at the beginning of apyrexia, shows the small, round or actively motile bodies—their "plasmodia." A few hours before the attack begins, however, there occurs a change;

there may be seen: (1) Small round bodies with a little mass of haemoglobin or pigment granules in the centre—ring-like forms; (2) small, more or less amoeboid bodies, with one or two extremely minute pigment granules; (3) larger, round, immovable parasites of a more glistening white color, with a round pigment block in the middle or at the periphery. The haemoglobin of the red corpuscle is, in some instances, concentrated about the parasite in the middle of the corpuscle, while the periphery is decolorized. Many of the corpuscles containing plasmodia are also shrunken, somewhat crenated, and of a color resembling old brass (globuli rossi ottonati). In quartan and tertian fever segmenting forms are commonly seen in the circulating blood; in this type of fever they are extremely rare. They are common, however, in the internal organs, particularly in the spleen and, in pernicious cases, often in the cerebral capillaries. Segmentation occurs while the parasite is yet in the red corpuscle which rapidly disintegrates. Pigmentation begins shortly before the paroxysm, and the discovery of pigment in the organisms is a sure sign that the paroxysm is near. The cycle of development appears to last about twenty-four hours or even less. With the paroxysms, and a few hours afterwards, appears the new group of young, fresh, hyaline bodies. They describe the crescents, admitting what they previously had denied, that these appear to have a double contour. They have seen intermediate forms between their plasmodia and the crescentic bodies. They find, as did Councilman, more crescents in the spleen than in the peripheral blood, and agree with Laveran that they are more common after continued attacks. They have, however, seen pernicious cases without crescents. They have never seen evidences of segmentation in the crescents; those bodies which are described by others they believe to be degenerative forms, asserting that what Canalis has considered to be fresh segments, are only vacuoles. In some instances the parasite may run its entire course to segmentation without the development of pigment. They conclude that, in the malarial fevers of the summer and fall in Rome, there occur, generally, daily or frequently repeated paroxysms with a tendency to become pernicious. With this type of fever is associated the presence of a small amoeboid parasite in the red-blood corpuscles. This organism shows a short cycle unaccompanied by the development of pigment, and a longer cycle, where a few pigment granules are to be seen. This parasite differs from the larger tertian and quartan organisms, which are found only in particular regions, and cause the milder forms of fever. Different malarial parasites are, then, related to the different times of the year, to different malarial regions, and, finally, to the mild and severe forms of the disease.

These observations have been confirmed in their main features by a large number of observers. Among the first were Gualdi and Antolisei,(111) who proved the existence of this separate type of organism by inoculation experiments.

Antolisei and Angelini (119, 131) refer to this variety of the parasite as the "haematozoon falcifòrme." They believe that it may run through its cycle of existence quickly, reaching the stage of sporulation, in some instances, before the appearance of pigment, as described by Marchiafava and Celli. In other instances it pursues a longer course, developing into the ovoid and crescentic bodies. They confirm Canalis' observations concerning the sporulative and degenerative forms observed in the crescents. The process of gemmation, however, they do not consider reproductive, likening the small, hyaline buds to the "corpuscles d'exudation" of Hayem. Golgi (94, 118) notes that some fevers with long intervals are associated with these organisms, and believes that they are particularly related to the crescentic forms which pursue a slow development, the paroxysms thus occurring far apart.

Patella,(141) Terni and Giardina,(145) Bastianelli and Bignami,(168, 170) Sanfelice (190) in Italy, Grassi and Feletti (122, 205, 221, 339) in Sicily, Mannaberg,(291) von Jacksch (128) in Austria, Plehn (262) and Kamen (343) in Germany, Sacharow,(153) Korolko,(236) and Titow (177) in Russia, Dock,(207) one of the writers of this article,(327) and Koplik (305) in America have confirmed, in the main, these observations, in so far as they recognize a distinct type of organism associated with the aestivo-autumnal fevers, an organism which differs from those observed in the regular tertian and quartan ague. Considerable difference of opinion exists, however, between these observers as to the significance of certain forms, particularly the crescentic bodies. Bignami,(179) Bastianelli,(168, 170) and Marchiafava and Celli,(222, &c.) in their later works, assert, in contradistinction to the views above expressed, that the crescentic and ovoid pigmented bodies are deviate and degenerate forms; that their presence in the blood has no influence on the condition of the patient. They deny the possibility of sporulation in these forms, but state that they can follow out processes of vacuolization, fragmentation (gemmation) and flagellation, all of which they believe to be degenerative processes. Certain authors have gone beyond this simple division, and have sub-divided the class of "aestivo-autumnal" organisms. Marchiafava and Bignami (218, 245) believe that they can separate two distinct varieties of the aestivo-autumnal parasite. Each is represented in the beginning by a small, hyaline, amoeboid, or ring-shaped body, but the cycle of development, in the one instance, lasts about twenty-four hours, and in the other about forty-eight hours. In other words they recognize a true *quotidian* and a "*malignant tertian*" type of organism. The *quotidian* fever they say may be quite regular, the attacks being definitely intermittent and similar in most ways to those of the double tertian or triple quartan fever, lasting from six to eight, or rarely twelve hours. Usually, however, the attacks do not come at regular intervals, showing often a tendency toward anticipation or retardation, and varying in severity and duration; often a more or less continuous fever may result. The parasite of this quotidian fever passes a good part of its existence as a small, amoeboid, hyaline body. It may then pass on directly to segmentation with but little increase in size, though, generally, it develops a few fine pigment granules in its protoplasm before this occurs. In either case the segmentation occurs within the red blood corpuscle before this is definitely destroyed. Sporulation occurs almost entirely in the internal organs; the appearance of segmenting bodies in the circulating blood is rare. In the spleen, however, they may be found in great numbers. The corpuscles containing the parasites are often shrunken and of a brassy color; the retraction of the haemoglobin about the parasite, as described by Marchiafava and Celli, may be present. After a certain length of time crescentic and ovoid forms usually appear.

The *tertian* type of organism is associated with a fever which, according to Marchiafava and Bignami, has a characteristic type, differing materially from the mild or spring tertian. The individual paroxysm lasts usually more than twenty-four hours, often from thirty to forty hours. There is a marked tendency toward aggravation, anticipation, and conjunction of the attacks which frequently follow one another in such a manner as to produce a continued fever. They believe, however, that they are able to distinguish certain characteristic points about the febrile curve; a rapid invasion, a status febrilis, with more or less marked oscillations, a slight pseudo-crisis, a pre-critical rise in temperature during which the maximum point of fever is often reached, and finally the crisis. The paroxysms are so long and the periods of apyrexia so short that the patient often believes that he is suffering from a continuous fever, while, from various modifications of the temperature curve, this may actually be the case. Generally the curve becomes more or less complex; this may be brought about by various influences.

(1). *By modifications of the curve in the individual paroxysm;*

(2). *By modifications in the succession of the paroxysms.*

(1). *The important modifications of the curve* are the following:

(*a*). The lack of a sharp initial elevation so that the curve rises in a progressive and continuous manner;

(*b*). the exaggeration of the pseudo-crisis so that the attack tends to lose its individuality;

(*c*). the prolongation of the paroxysm, which is usually associated with an exaggeration of the thermic oscillations during the fastigium;

(*d*). the lack of a sharp pre-critical elevation.

(2). *The modifications in the succession of the paroxysms* may be:

(*a*). The anticipation of the paroxysms, which can occur in the mild as well as in the severe forms;

(*b*). the retardation, which can occur also in the grave infections;

(*c*). the prolongation of the paroxysms, by which apyrexia is made incomplete;

(*d*). the presence of slight oscillations in the temperature during the period which ought to be one of apyrexia; the reduplication of the attacks.

Further irregularities in temperature may be caused by combined infections or by the use of quinine or other remedies.

The parasite which is the cause of this type of fever pursues its cycle of development, according to their idea, in direct relation to the clinical course of the case, just as do the other varieties of the malarial parasite. Its development is very similar to that of the quotidian parasite. It produces, however, a larger quantity of pigment, and, at the time of its full growth, may be one-half the size of the red corpuscle. The reproductive processes take place in this form as well as with the parasite of quotidian fever, chiefly in the internal organs, and, at the beginning of the attack, it may be almost impossible for several hours to find any malarial parasites in the blood. One sees here, as with the quotidian parasite, the collection of pigment in a clump in the central part of the body which breaks up into segments while it is yet contained within the red corpuscle, which is almost invariably gravely altered—shrunken, crenated, brassy-colored or destroyed. The chief differences between these two varieties of the parasite, Marchiafava and Bignami state to be the following:

(1). *The length of the cycle of development,* which, in the quotidian parasite, lasts about twenty-four hours, and often occurs without the development of pigment, while in the tertian it lasts forty-eight hours, and is always associated with pigmentation.

(2). *The size of the amoeba;* in the same relative stage of development, the amoeba of tertian fever is generally larger and of a more transparent appearance.

(3). *The movements,* which, in the tertian parasite, are retained for a longer time by the larger pigmented forms than in the quotidian parasite; they are also more active in the tertian organism.

(4). *The length of the amoeboid unpigmented stage,* which, in the tertian body, may last more than twenty-four hours.

(5). *The time elapsing after the beginning of the new paroxysm, before the appearance of the new generation of parasites,* which, in the tertian fever amounts to several hours, considerably longer than with the quotidian type.

The differences between the malignant tertian parasite and that of the ordinary mild tertian fever are marked.

(1). It differs in its *size,* which is considerably smaller than that of the organism of mild tertian fever.

(2). In the *appearance of the young forms,* which, in the malignant tertian fever, are ring-shaped, a characteristic not observed in the mild tertian fevers.

(3). In the *character of the pigment,* which, in the organism of mild tertian, is always active, which is not the case in this form; the *quantity* of pigment in the malignant tertian organism is also much less than in the spring tertian body.

(4). The *manner of segmentation;* the segmenting bodies in mild tertian parasites are larger and contain a greater number of spores than those of the malignant tertian organism; they are also found very frequently in the blood of the finger in the one instance, and very rarely in the other.

(5). *The changes occurring in the infected red blood corpuscles;* in the spring tertian these become increased in size and decolorized, while in aestivo-autumnal fever they commonly assume a deeper brassy color and become shrunken and crenated.

(6). Finally, with the amoeba of the aestivo-autumnal tertian is associated the *appearance of crescents* which never occur in the other form.

A still more elaborate classification of the malarial parasite is that of Grassi and Feletti.(221, 339) These observers separate the parasite into five distinct varieties:

(1). The "Haemamoeba praecox," giving rise to quotidian fever with a tendency to anticipation.

(2). The "Haemamoeba immaculata," which is similar to this, excepting that it runs its course sometimes more rapidly without the development of pigment.

(3). The "Haemamoeba vivax," giving rise to tertian fever.

(4). The "Haemamoeba malariae," giving rise to quartan fever.

(5). The "Laverania malariae," giving rise to the irregular fevers.

They insist that the Haemamoeba praecox, which corresponds to the aestivo-autumnal parasite of Marchiafava and Celli, is an entirely separate organism from the crescentic and ovoid forms, to which they give the name of "Laverania malariae." They agree with Canalis, Golgi, Antolisei and Angelini in believing that segmentation may occur in these forms. They have made extensive studies, in the blood of birds, of the haematozoa which so closely resemble the parasites of malarial fever, and they believe that the parasites of the bird and those of the human being are entirely similar, though inoculations from one to the other have proven unsuccessful.

Sacharow,(212) in Tiflis, describes a "parasite of irregular fever" which corresponds to the aestivo-autumnal type of organism, the only difference being in the greater frequency with which segmenting bodies are to be found in the peripheral circulation. He believes, as do Grassi and Feletti, that the crescentic bodies form a separate type of the parasite; they are associated with irregular fevers. He adopts the following types:(276)

(1). Haemamoeba praecox (Grassi).
(2). Laverania (Grassi).
(3). Haemamoeba febris tertianae (Golgi).
(4). Haemamoeba febris quartanae (Golgi).

Mannaberg (291) has pursued quite elaborate studies of the malarial parasites, and has reached results which are not uninteresting. He divides the parasites into two groups:

(1). *Malarial parasites with sporulation and without syzygia:*
(*a*). The quartan parasite.
(*b*). The tertian parasite.
(2). *Malarial parasites with sporulation and syzygia:*
(*a*). The pigmented quotidian parasite.
(*b*). The unpigmented quotidian parasite.
(*c*). The malignant tertian parasite.

It will thus be seen that he accepts the division of Grassi and Feletti into the pigmented and unpigmented quotidian parasite (the Haemamoeba praecox and the Haemamoeba immaculata). The descriptions which he gives of these bodies are exactly similar to those given by Marchiafava, Celli and Bignami. The great difference, it will be seen, between Mannaberg's classification and that of the Italian observers, is due to his interpretation of the crescentic bodies. These bodies, he asserts, arise from a conjunction of two smaller, intra-corpuscular forms. This conjunction is followed by the development of a membrane about the body; more pigment is formed, and finally the full grown ovoid or crescentic body results. By his staining methods he believes that he obtains definite proof that the crescents represent two individuals. He has seen the division of a crescentic body into its original two constituents. Beyond this transverse segmentation, as he calls it, he has never seen any other evidence of segmentation of the crescents. He denies, however, the assertion of Bignami, Bastianelli and Marchiafava that these are degenerate forms.

Dock (240) has been able to satisfactorily distinguish the tertian, quartan and aestivo-autumnal organisms without any sub-division of the latter variety.

Titow (177) confirmed in the main Golgi's divisions of the parasite, which Korolko (226) has also been able to do.

One of the authors (327) of this note has also been able to confirm the divisions into the tertian, quartan, and aestivo-autumnal varieties.

Finally Golgi (300) has studied the aestivo-autumnal fevers at Rome, arriving at results somewhat different from those of most other observers.

He asserts that "the doctrine of the nosogenic process of the malarial fevers is not yet entirely known." Marchiafava's and Bignami's ideas concerning the regular cycles of twenty-four and forty-eight hours are rather an hypothesis than a fact based upon actual observation. His own observations have led him to believe that:

(1). The parasites which circulate in the peripheral vessels in aestivo-autumnal fever are nothing more than an index, "non necessarie," though almost constant, of the infection; they have of themselves little to do with the pathogenesis of the febrile process; they represent the first phases of a cycle of development which is much longer than has been believed—of as yet undetermined duration.

(2). The entire process of development occurs, not in the peripheral blood circulation, but in the internal organs; here these parasites go through their diverse stages of development.

(3). The doctrine of the quotidian and tertian varieties is not borne out by his researches; "it is not justifiable to accept this classification."

He confirms Baccelli's (263) observations that, in the first few days of the disease, comparatively few organisms may be found in the circulating blood; they may indeed be absent. Those forms which one does find represent only the earliest phases of development. He distinguishes three phases:

(1). The small amoebae without pigment or with but a few granules—the forms seen in the circulating blood.

(2). The small amoebae with central clumps or blocks of pigment, which are thought to be pre-segmenting forms, and forms of more advanced development which may have grown to a size as large as the red blood corpuscle which may have been wholly destroyed. This phase is doubtless longer than the first.

(3). A phase represented by the parasites with marked endoglobular development or even free forms. These present different appearances depending on their ultimate development and particularly on the forms of sporulation which are various.

There are three main varieties of segmenting forms:

(*a*). Regular forms like those of the tertian and quartan organisms; these may vary greatly in size, some being larger than the red blood corpuscles, with as many as forty or fifty segments.

(*b*). Forms of endogenous segmentation, where a layer of substance looking like a membrane remains about the periphery, while within there are eight, to ten, to twelve small spherules with sharp contour, arranged irregularly about a pigment block.

(*c*). Forms with a more advanced development. These may vary from one-third the size of a red blood corpuscle to a size even larger than the corpuscle itself. They always contain a pigment mass. They have an irregular, mulberry-like contour and can change their form; they arrive at reproduction in various manners.

Segmenting bodies are best found from three, to four, to five, to six hours before the paroxysm, but, as the organisms appear to be arranged in foci in the spleen—here a group in one stage of development, here in another—the puncture of the spleen gives uncertain results.

Certain facts suggest that these organisms may continue to develop and even segment within the bodies of large macrophages in the spleen. This, however, and many other points, need further investigation.

He divides the malarial fevers into two groups:

(1). Fevers, the pathogenesis of which is connected with parasites which have their principal habitat in the circulating blood where, by preference, they accomplish the phases of their cycle of existence.

(2). Fevers, the pathogenesis of which is connected with parasites which have their chief seat in the internal organs, particularly the bone marrow and the spleen, where, by preference, they accomplish their cycle of existence in conditions of relative stability.

(1). The fevers of the first group are, unquestionably, associated with different species or varieties of the parasite:

(*a*). *The quartan parasite.*

(*b*). *The tertian parasite.*

(2). "To the second group belong the fevers which appear clinically under multiform types, very often irregular, of which for the present it is impossible to make a grouping based upon an ascertained biology or cycle of development of the parasite. . . . We are dealing, in these cases, with generations of parasites which, occurring in the parenchyma of organs, in different stages of development, give origin, at periods of a certain regularity, or, in a more or less continuous succession, to colonies of young forms which, in large or small numbers, or in insignificant quantity, may escape into the blood current, permitting one to discover by microscopical examination of the blood the presence of the small endo-globular amoebae." He refers to the crescents as "forms the biology of which has not yet been well determined."

CULTURE AND INOCULATION EXPERIMENTS.

Thus we see that all authors who have had sufficient material at their service, agree in the statement that malarial fever is always associated with the presence of these parasites in the blood. It is, however, unfortunately true, that this discovery fills but one of the classical stipulations of Koch, which go to prove the dependence of a disease upon a specific micro-organism.

Attempts, by many observers, to cultivate the parasite, by the most varied methods, have proven uniformly unsuccessful. Coronado,(273, 297) alone, asserts that he has been able to cultivate the organisms in water from a source from which he believes many individuals had been infected. Sterilization of the water makes cultivation impossible. By introducing malarial blood into tubes containing some of this water with about one-third the volume of mud from the bottom, he obtains, in twenty-four hours, cultures in which, he believes, he can trace the entire development of the malarial parasite. He observes the development of flagella from the pigmented parasites; these become free, and, eventually, break into from eight to fifteen small segments which begin again the cycle of existence developing pigment (!) and arriving, finally, again at the stage of flagellation.

These remarkable experiments have been repeated by Sacharow (334) without success.

If, however, culture experiments have failed, some observers have, at least, succeeded in preserving the organism for a certain length of time, outside the human body. This was first accomplished by Sacharow,(163) who was able to keep the parasites (aestivo-autumnal (?)) alive as long as a week in leeches which were kept on ice. Rosenbach,(214) applying leeches to a case of tertian fever, was able to demonstrate apparently living organisms after forty-eight hours. He believed that the parasites showed signs of growth and, possibly, of multiplication. Sacharow (324) has repeated these experiments, in order to test the effect of cold on the parasites, with interesting results. He placed the leeches on ice, examining them at varying periods. With the aestivo-autumnal parasite he still found forms with actively amoeboid movements and normal staining reactions after seven days, while an inoculation experiment made on the fourth day was successful. In a case of double tertian fever he found, after forty-eight hours, only the small amoeboid initial stages of the parasite, the older forms being apparently less resistant to the cold.

All experiments, then, directed toward the cultivation of the parasite, with the exception of the as yet unconfirmed work of Coronado, have failed. Experiments, however, with inoculations made, if not from pure cultures, at least from patients whose blood has been carefully examined before and after the inoculation, have given results which tend, strongly, not only to show that these parasites are the specific cause of malarial fever, but also to uphold the view first introduced by Golgi, that certain definite varieties of parasites are associated with certain definite varieties of fever. Gerhardt (38) was the first to show that malarial fever could be transmitted by inoculation of one patient with the blood of another. His results, however, were obtained before the parasite itself had been discovered. In two instances, inoculations were made from patients with quotidian paroxysms. In the first, quotidian paroxysms appeared in sixteen days; in the second, irregular paroxysms gradually becoming quotidian appeared on the sixth day. The inoculation consisted in the injection of a Pravaz syringe full of blood.

In 1884, Mariotti and Ciarrochi,(39) and Marchiafava and Celli,(41) inoculated five patients with malarial blood, obtaining positive results in three cases. Unfortunately though, as, in all these instances, several inoculations were made, it is impossible to state the exact period of incubation. It is interesting, however, to note, that, in case I, chills developed eleven days after the first intra-venous inoculation, a subcutaneous inoculation having been entirely negative before; in the second case, twelve days after the first inoculation; and in the third, thirteen days after the first inoculation. Though these facts were not interpreted in exactly this manner by the authors, it is in every way probable, in view of what we have later learned, that this represented the true incubation period.

The next experiments were reported by Gualdi and Antolisei (102) from Baccelli's clinic at Rome. Two patients were inoculated intravenously with 3 ccm. of blood from a patient suffering with quartan fever, at a time when the blood showed the earlier stages of segmentation. In the first case an irregular fever appeared in ten days after the inoculation, the blood showing the organisms characteristic of aestivo-autumnal malarial fever. In the second case the inoculation was followed, in twelve days, by a mild irregular fever, the blood showing, as in the former case, aestivo-autumnal organisms, but, also a few quartan forms. These two cases have served and still serve as the strongest argument used by the opponents of the idea that definite types of organisms are associated with definite types of fever. For here are two cases of aestivo-autumnal fever with its characteristic organism, resulting from inoculation with the blood of an apparently pure case of quartan fever. It was, however, discovered, on more careful investigation, (110) that the patient from whom these inoculations were made, was not suffering from his first attack, but had previously suffered from irregular fever, and, later on, had had a relapse, the blood showing the characteristic organisms. In view of the results which have been obtained since then, one is certainly justified in accepting the opinion of the experimenters themselves, as expressed later, that this case was not one of pure quartan infection, and that the aestivo-autumnal organisms being more resistant had developed to the exclusion of the quartan parasites which were present at the same time.

Later, Antolisei and Angelini (103) inoculated two patients with the blood from a case of tertian fever. In each instance, in eleven days, within a few hours of one another, the two inoculated patients showed a rise of temperature, and, in each instance, characteristic tertian organisms were found. In the first instance, however, the fever was of an anticipating character, and later on became quotidian, while in the second case, the fever was at first somewhat irregular, but later showed a tertian character. The irregularity of the fever in the second case they ascribed to the presence of more than one group of organisms.

Gualdi and Antolisei (110) next report a typical case of quartan fever, in which the characteristic quartan paroxysms, with the usual organisms appeared twelve days after the inoculation. The same authors (111) later made an inoculation from the blood of a patient who had had malarial fever of an irregular type, with small hyaline bodies and crescents in the blood; the hyaline bodies had, however, disappeared under quinine, and after two days' careful examination of the blood by Marchiafava and Celli, nothing but crescentic organisms were found. Irregular fever began on the ninth day, ring-shaped and hyaline organisms were seen on the tenth day, and eight days later, after the administration of quinine, crescentic bodies were for the first time seen; 2 ccm. of blood were used in the inoculation.

Di Mattei (203) injected, intra-venously, blood from a case of irregular fever where he found at first only crescents, into a patient who had suffered from quartan fever which had disappeared spontaneously. A few days after inoculation hyaline bodies without pigment were found. Sixteen days after inoculation irregular fever appeared, and nine days later, crescentic bodies were found in the blood. He then injected blood from a case of quartan fever into a patient whose blood showed crescents. In fifteen days the symptoms of quartan fever appeared, the blood showing typical quartan organisms, while the crescents diminished in number, and finally disappeared.

Calandruccio (205) inoculated himself with blood from a case of quartan malaria, which, at times, had shown regular quartan paroxysms, and, again, evidences of a triple quartan infection. He injected about 1 cc. of blood, with a sterilized Pravaz syringe, into the subcutaneous tissue of his left arm. Eighteen days later he developed a malarial fever, the blood showing organisms similar to those injected, the fever pursuing the same course. He had never had malaria previously, and had never lived in a malarious district. The case from which the blood came was also one of artificial infection. In two other cases Calandruccio obtained positive results from the inoculation with blood containing only crescentic bodies. The time of incubation, was, however, not noted.

Bein (228) made four experiments with tertian parasites. In the first instance, one of tertian fever, a quotidian ague with characteristic tertian organisms appeared on the twelfth day. In the second experiment, a case of quotidian fever with tertian parasites gave rise, in twelve days, to a similar fever with similar organisms. In the third instance a double tertian infection gave rise, in nine days, to a single tertian.

Blood from the same case, injected into a fourth patient gave rise, in nine days, to tertian paroxysms disappearing spontaneously and recurring, after six days, as quotidian fever. In this, as in all the other cases, characteristic tertian organisms were present. The blood, in these instances, was taken in leeches which were then placed in warm water, and opened with sterilized scissors in a sterilized dish; the blood was taken up in a Pravaz syringe and injected intra-venously in one instance, and in the other cases, into the subcutaneous tissue of the forearm.

Baccelli (263) made intra-venous inoculations from a case of double tertian fever and from a case of quartan fever, reproducing, in each instance, the same type of fever and of organism. The period of incubation in the case of tertian fever was six days, in the quartan eleven days.

Sacharow (324) performed an interesting experiment upon himself. He obtained blood in leeches from a case of pernicious, comatose malaria with large numbers of hyaline, ring-shaped and amoeboid, non-pigmented bodies. From one of these leeches, which had been kept on ice for four days, 1 ccm. of the blood was injected, subcutaneously, into the arm. Twelve days later chills and fever appeared, two paroxysms occurring on successive days. On the second day characteristic ring-shaped hyaline bodies were found in the blood. On this date quinine was administered and the organisms and fever disappeared.

The results of these inoculation experiments are certainly striking. In only two instances has the type of organism which was believed to have been introduced, failed to reappear in the blood of the infected individual. These were the first two cases of Gualdi and Antolisei; the probable cause of this variance has already been explained. In all other instances the same type of organisms has appeared, and, with the exception of the instances where infection from a case of apparently single tertian fever produced a double tertian infection, and the converse, the types of fever have been exactly what might have been expected. The average duration of incubation, estimated from these eighteen cases, would appear to be from 11 to 12 days. In individual cases there was a variance of from 6 to 18 days. The experiments of Di Mattei, showing the disappearance of one set of organisms upon the introduction into an already infected individual of blood from a patient suffering from a different variety of infection, are very interesting. They show the possibility of producing, experimentally, the presence of two varieties of organism at the same time, but they show also, how, in each of the cases, the symptoms were produced by one variety only, the growth and development of one set of organisms being associated with the disappearance or diminution of the other. Bacteriologically occurrences similar to this are, of course, not uncommon. It will be interesting to note, further on, that in the 11 cases of combined infection which we have observed, one variety of organism has always been in great predominance, while the symptoms have appeared to be due to this set alone. We have never seen a combined infection with irregular fever which appeared to be due to the flourishing of two varieties of organisms at the same time.

Dochman,(11) in 1880, reported some interesting results from inoculations with the contents of herpetic vesicles in cases of malarial fever. In three cases typical intermittent fever resulted; the fever was quartan in one instance, tertian in another, and quotidian in the third. In all instances, however, the fever began, either on the same day, or on the day following the inoculation; no examinations of the blood were made. These experiments have never been confirmed, while careful examinations have failed to reveal the presence of organisms in the herpetic vesicles or in sweat.

METHODS OF EXAMINATION OF THE BLOOD.

The most satisfactory method, in many ways, of studying the malarial parasite, is in the fresh blood which contains the organisms while yet living. The preparation of such specimens is extremely simple. A minute drop of blood is taken upon a cover glass and allowed to fall upon a clean slide; no pressure is exerted upon the glass, and the specimen is immediately examined. Some observers surround the edge of the glass with vaseline or paraffine in order to prevent evaporation. Some make use of Hayem's special slide, in which a small area in the middle is surrounded by a slight circular depression. A more accurate description of the methods of examining fresh blood will be given later, when we speak of our own proceedings.

One method of examining fresh blood we will speak of here as interesting, and, possibly, of value. We cannot, however, speak from experience. Plehn(176) asserts that he has obtained the best results in the following manner: All examinations of the blood are made at body temperature, the microscope, as a whole, being placed within a specially constructed case made by Lautenschläger of Berlin. He makes use of an ordinary slide, in the middle of which an area about the width of a common cover glass is surrounded with a layer of shellac, thus forming a modified hollowed slide. A carefully-cleaned cover glass is then covered by a drop of fluid paraffine, while another drop is allowed to fall in the middle of the concavity of the slide. The well-cleaned finger-tip, from which he takes the blood, is then painted with pure vaseline in order to prevent the entrance into the blood of foreign substances which might injure its composition. Through this vaseline he makes his puncture collecting the blood, immediately, upon the fresh paraffine drop on the cover glass. This is then laid upon the slide so that the blood spreads out between the two layers of paraffine which protects it from outside influences. In this manner he has seen the blood well preserved for two or three days. The difficulties of this method, it is easy to see, would prevent its daily use in ordinary examinations for diagnostic purposes.

Many different methods have been proposed for the staining of the parasite and for the preparation of permanent specimens. The parasite is well colored by all basic aniline dyes, in fact, by most nuclear stains; it is not colored by the acid aniline dyes. It would be a waste of space to enter into a careful description of all the methods which have been advised. We will take up here but a few of the more important.

The most satisfactory color, upon the whole, for the staining of the parasite is generally acknowledged to be methylene blue, and most observers have obtained the best results by a combination of methylene blue and eosin, the eosin staining the red corpuscles, the methylene blue the parasites.

For making permanent specimens, the blood is collected upon cover glasses and fixed, either by heat or by subjection to the influence of absolute alcohol or alcohol and ether combined in equal quantities.

Chenzinsky(75) recommends the following method: A concentrated watery methylene blue solution, diluted one-half with water, is mixed with an equal volume of a ½ per cent. solution of eosin in 60 per cent. alcohol. The dried and fixed cover glass specimens are allowed to remain four or five minutes in the staining fluid, and then washed in water, mounted in balsam, and examined.

Celli and Guarnieri (98) recommend an ingenious method which gives, apparently, good results. They endeavored to stain the parasites while yet alive, their mixture consisting of a solution of methylene blue in fluid from a serous transudation. They collected ascitic serum in sterilized test tubes under aseptic methods. The tubes were filled about two-thirds full of serum to which a sufficient quantity of methylene blue was added. This, for a short time, floats upon the surface, and then sinks slowly to the bottom, coloring the fluid a deep blue. After filtering into another test tube, the solution will remain for a long time without changing. Neither microscopical examination nor cultures reveal, after several days, the presence of micro-organisms. To color the blood in the fresh state the finger of the patient is cleansed and punctured with a needle, while, with a glass rod, a drop of the staining fluid is placed upon the drop of blood which appears. From this mixture a drop is placed upon a cover glass and allowed to spread out upon the slide, a little pressure being exerted in order to spread out the red corpuscles and prevent the formation of rolls. The staining requires a little time, the best results being obtained by leaving the preparations from one to three hours in a moist chamber. These specimens are, of course, not entirely permanent.

Feletti (171) advises the following method: A small drop of an alcoholic solution of methylene blue—one part to five—is placed upon a slide and allowed to dry by passing the glass over a flame. One drop of blood is collected upon a cover glass and placed upon the stained area; the cover glass is surrounded by paraffine. The methylene blue is redissolved in the blood serum and stains the parasites satisfactorily.

Plehn (176) advises the following method. The solution which he uses is constituted as follows:

Concentrated aqueous solution of methylene blue	60.
One-half per cent. eosin solution in 75 per cent. alcohol	20.
Distilled water	40.
20 per cent. NaOH	gtt xii.

The cover glass specimens are allowed to remain in absolute alcohol for from three to five minutes, are then placed in this solution for from five to six minutes, washed in water, and mounted.

The results obtained by this method are excellent, and specimens may be obtained as permanent as is possible by the use of eosin and methylene blue.

Mannaberg(201) advises the following method: The dried specimens are allowed to remain for half an hour in a mixture of absolute alcohol and ether of equal quantities, dried upon filter paper, stained in a concentrated watery solution of methylene blue for half an hour, washed with water, dried on filter paper, and colored for about half an hour in a 2 per cent. solution of eosin in 60 per cent. alcohol, washed in water, dried, and mounted in balsam.

Romanowsky(210) advises the following method: He keeps two solutions on hand; a saturated aqueous solution of methylene blue, and a one per cent. watery solution of eosin. The older the methylene blue solution the better the results. The specimen is heated not less than thirty minutes at a temperature of from 105° to 110° C.; the staining mixture is then made just before it is to be used. To one part of the filtered methylene blue solution about two parts of the eosin solution are added. This is carefully stirred with a glass rod, but not filtered, and poured into a watch glass. The cover glasses are allowed to float upon the top of this fluid, the specimens being covered by another inverted glass, and the whole by an inverted cylinder which is moistened upon the inside. In from one-half to three hours—best in two or three hours—good specimens are obtained.

Romanowsky believes that he obtains thus three colors; the red corpuscles are stained red by the eosin, the malarial parasite of a Prussian blue color by the methylene blue, and the nuclear chromatin of a violet color—a neutral stain.

Malachowsky(211) advises the following method: The dried specimens are fixed by being placed in absolute alcohol for several minutes, and then allowed to remain twenty-four hours in Sahli's borax methylene blue solution:

Concentrated aqueous solution of methylene blue	24.
5 per cent. solution of borax	16.
Water	40.

Filter after twenty-four hours.

Sacharow,(212) in studying the small hyaline bodies of aestivo-autumnal fever, advises the use of gentian violet on account of the intense color which the parasites take.

Sforza(288) has used the method of Canon and Pielicke with good results. The dried specimen is fixed by being placed for from five to ten minutes in absolute alcohol. It is then allowed to remain for from six to twenty hours in the following solution at 37° C., washed in water, and mounted. The solution is as below:

Concentrated aqueous solution of methylene blue	40.
¼ per cent. solution of eosin in 75 per cent. alcohol	20.
Distilled water	40.

Laveran(290) advises the following simple method: The dried specimen is fixed in a mixture of alcohol and ether, equal parts, stained for thirty seconds in a concentrated aqueous solution of eosin, washed in distilled water and dried. It is then stained for about thirty seconds in a concentrated aqueous solution of methylene blue, washed again, dried and mounted, either dry or in Canada balsam.

Good results may be obtained by the use of haematoxylin, Mannaberg,(291) in particular, advising this method. His method he describes as follows: "The dried specimen is allowed to float at first for about five minutes upon distilled water, dried between filter paper, and washed in a very dilute solution of acetic acid (acetic acid gtt. j; distilled water 20 ccm.) until complete disappearance of the haemoglobin. The entirely colorless preparation is then floated for two hours upon the fixing solution:

Concentrated aqueous solution of picric acid	30.
Distilled water	30.
Glacial acetic acid	1.

From this it is placed in absolute alcohol for about two hours. This is followed by staining for twelve to twenty-four hours in alum haematoxylin; then by differentiation by means of 0.25 per cent. HCl alcohol (alcohol 75 per cent.) and ammonia alcohol (3 drops of ammonia to 10 ccm. 75 per cent. alcohol), washing in 8 per cent. alcohol, mounting in Canada balsam. The washing of the preparation with water and acetic acid causes the removal of all albuminous substances which would otherwise give rise to annoying precipitates with the subsequent treatment with picric acid. The preparations made by this method show the parasites as well as the leucocytes of a blue color. The red blood corpuscles remain perfectly colorless. In satisfactory preparations the finer structure of the parasite stands out very beautifully."

Mannaberg uses a solution of haematoxylin (10 grammes of haematoxylin to 100 of absolute alcohol) which is as old as possible. Before use, one part of this is mixed with two parts of a ½ per cent. ammonia alum solution.

The fixing of specimens with osmic acid and a large number of other methods which have been advised will not be entered into here. References may be found in the table of literature at the end of the article.

THE FINER STRUCTURE OF THE MALARIAL PARASITE.

Celli and Guarnieri(98) were the first to make a careful study of the intimate structure of the malarial parasite. In the fresh state definite signs of a nucleus are not to be made out. In their specimens colored with methylene blue dissolved in ascitic fluid, they were able to distinguish a deeply colored ectoplasm and a more palely stained endoplasm. The bodies which appear to be ring-shaped, are not really rings, the part within the ring being represented by the endoplasm which is but faintly colored and allows the corpuscle to show through. In the youngest bodies they noticed a deeply staining spot at a point on the border between the endo- and ectoplasm. In the endoplasm, in some specimens, they were able to make out a palely stained body or sometimes one or more sharply stained points or a net-work, which they believed to be the nucleus. They describe the double contour of the crescents and note that these bodies stain more deeply toward the extremities, while the middle is pale; often there is a spot under the pigment in the middle of the crescent which takes a deeper color.

Grassi and Feletti,(122) in their studies of the quartan parasite, go further, stating that the parasites possess a large, clear, bladder-like nucleus, corresponding apparently to the entire endoplasm described by Celli and Guarnieri. This is usually eccentric, with a delicate, often invisible nuclear membrane. The nuclear juice they believe to be "halbfest;" while the nuclear net-work consists of a more or less eccentric nucleolus-like mass of varying form, sometimes round, sometimes almost triangular or quadrangular, from which three or four very delicate fibres which are almost invisible in the smaller forms, stretch out toward the membrane. The plasma is generally hyaline, but often shows a fine granulation which stains readily with methylene blue; it also shows the granules of melanin. There are sometimes one or more non-contractile vacuoles. As the body grows the nucleolus grows larger and almost fills the nucleus; it often has a rod-like shape. This divides into two parts, and each daughter section again dividing, there results, finally, an amoeba with numerous nucleolus-like granules. Eventually nuclear juice collects, and a thin, delicate membrane forms about each nucleus. Later on the plasma divides in a manner not yet entirely cleared up, the pigment remaining behind, leaving the fresh segments, which they believe to be gymnospores, probably simply young amoebae.

The crescents have a similar nucleus in the middle, about which the pigment is usually collected. The crescent is surrounded by a membrane which, they believe, arises from the blood corpuscle in which it has developed, as does the delicate membrane surrounding the segmenting bodies. The plasma (ectoplasm) alone is concerned in the formation of flagellate bodies, the nucleus taking no part; this fact, they believe, is sufficient to prove that these forms are not regenerative in nature.

Celli and Sanfelice (190) likewise describe the pale, non-staining nucleus.

Romanowsky (188, 210) studied the tertian parasite on dried cover glass specimens stained, by a particular method, with eosin and methylene blue. He separates, always, two distinct parts of the organism; one of irregular shape of a Prussian blue color; and one entirely uncolored of an ovoid or round form lying within the blue colored rim. In this central area, always close to the periphery, he found a small body of a dark carmine-violet color. Because these minute bodies were present in every parasite, and because they showed a coloring similar to that of the nuclei of the leucocytes, and because, also, they showed at times signs of a fibrillary metamorphosis, he believed that these represented the chromatic part of the nucleus while the rest of the clear central area was the clear nuclear fluid. He believes that at the time of segmentation he can distinguish karyokinetic figures in the chromatic substance of the nuclei.

Sacharow,(212, 324) studying the aestivo-autumnal organism, notes also the pale central area—nucleus—with the deeply staining granule—nucleolus. He states that as the organism approaches segmentation, with the collection of the granules into a central mass, the nucleus disappears.

Mannaberg(208, 291) states that the nucleus is represented in the unstained specimen by a refractive body which takes up the greater part of the spore; that the small, more refractive point within it represents the nucleolus; the clear space which one occasionally sees in the large free forms represents the bladder-like nucleus which Grassi and Feletti described in stained specimens. The nucleus is represented as a relatively large, more or less round, bladder-like affair which lies, generally, excentrically. It is colorless or only very slightly colored, and shows at a point on the periphery a deeply staining body about which one sometimes sees a more palely stained zone. This body, which contains the greater part of the chromatin substance, is the nucleolus, while the clear substance represents the nuclear juice. As the parasite grows one can distinguish an outer layer of protoplasm taking a deeper stain and showing the granules of melanin, and an inner clearer layer free from granules, lying about the nucleus. The nucleus is usually excentric. The nucleolus grows with the organism, but before segmentation it disappears, passing out apparently into the substance of the parasite. The nucleus at this stage has a diffuse pale blue color, and is only to be distinguished from the parts outside by its lack of pigment; at this time one may speak of a "plasma part" and a "nuclear part" of the parasite. With segmentation we begin to see, in the nuclear part, the appearance of new nucleoli which finally form the centres of new spores. He cannot confirm Romanowsky's views concerning the karyokinetic division. He divides the life of the parasite into a vegetative and a reproductive stage. The reproductive stage begins with the disappearance of the nucleolus.

More recently Bastianelli and Bignami(331) have studied minutely the structure of the aestivo-autumnal parasites. They fixed their specimens with alcohol, and stained with eosin and haematoxylin. According to them the young parasite consists of two substances;

an outer colored and an inner uncolored cytoplasm. In the former one sees one or more granules of chromatin though no real nuclear structure is to be recognized. The ectoplasm is in functional activity during the entire life of the parasite. During the further development of the body these three portions remain quite clear and distinct, while granules of melanin begin to appear in the cytoplasm. As the increase in size progresses the small granules or masses of chromatin substance disappear, entering probably into solution in the cytoplasm. The cytoplasm increases in quantity and shows a slightly granular or homogeneous appearance. At this time the endoplasm develops a slight staining propensity. The pigment then begins to leave the chromophilic zone and tends to collect toward the middle or at one side of the parasite; thus arise the small bodies with central pigment, bodies one-fourth to one-fifth the size of a red blood corpuscle. These bodies consist of an apparently homogeneous substance more deeply colored in its outer part than in the middle, but without sharp boundaries between the two substances. In this stage the phase of reproduction may suddenly take place, but often the bodies keep on growing, the chromophilic substance ever increasing in quantity; the largest individual forms however are always smaller than a red blood corpuscle. The largest forms which one sees free in the plasma and, especially, in the spleen show changes which lead the authors to believe that they are degenerative, and incapable of reproduction. The reproduction begins with the formation of very small, deeply colored points of thickening of the chromatin substance; these increase steadily in size, becoming, finally, round or slightly ovoid in shape. Later on each one of these chromatin bodies becomes surrounded by a fine border of chromophilic protoplasm. A small amount of faintly stained protoplasm remains apparently unused. These spores differ from the young parasites in (1) that they have a regular, constant form; (2) that they possess no apparent achromatic cytoplasm (with occasional exceptions); (3) that they are immovable. The authors conclude that one cannot recognize in this variety of parasites, any body which has the various constituents of a true nucleus. The granular bodies of chromatin which form a part of the cytoplasm and become dissolved in it when the body is ready for reproduction, bodies which form the most important part of the young spore, represent that part of the parasite which performs the function of the nucleus. The phase of a resting nucleus is wanting in this organism, probably because of its rapid cycle of development. The crescents, they say, stain faintly and usually take a diffuse color; often they have no chromatin granules. They have no membrane, and show, usually, no differentiation of the protoplasm. These facts convince the authors all the more that these are sterile forms of the parasite. It will be seen in this description that the chromophilic granule or granules are said to exist in the ecto-plasm of the parasite, while most of the above mentioned authors have assumed that it lies upon the border of the endoplasm.

No one has been able to distinguish with certainty a membrane about the malarial parasite. Antolisei (126) has described a double outline about the spores, while, as has been stated, numerous observers interpret the more refractive outline of the crescentic and ovoid bodies as representing a distinct membrane. Antolisei and Angelini (119) believe that this contains haemoglobin.

In summary, then, the substance of the parasite has, by careful study, been shown to consist of a more deeply staining outer part, which contains the pigment granules, and an inner part which is pale and non-staining, excepting for a small, more deeply colorable body which is usually situated close at one side on the border line between this area and the more deeply staining outer layer. This colorless area is generally interpreted as a bladder-like nucleus, the dot at one side representing the chromatin substance or the nucleolus. Bastianelli and Bignami can distinguish no body in the aestivo-autumnal organisms which has all the characteristics of a nucleus. While Grassi and Feletti, Mannaberg, Bastianelli and Bignami have been unable to distinguish characteristic karyokinetic changes at the time of division, Romanowsky believes that he has done so.

MANNER OF REPRODUCTION.

Most observers agree that reproduction may take place by sporulation, and even Laveran is inclined to-day to accept the process first described by Marchiafava and Celli (45) as one of the modes of reproduction. Some observers, Laveran, (229) Mannaberg, (291) Dock, (151) and Manson, (347) believe that the flagellate body may represent another method of reproduction. The fragmentation of the large, extra-cellular bodies, and the budding of certain crescentic and ovoid forms, which were thought, at first, to represent reproductive processes, are now believed by most observers to be rather degenerative than regenerative processes.

The spores resemble very closely the young individuals, differing from these chiefly in their lack of motility and in their regular form. Plehn (176) believes that they possess one or more flagella and asserts that he has seen them move about actively among the blood corpuscles.

Antolisei (126) describes a double contour.

CLASSIFICATION OF THE PARASITE.

Much has been written concerning the classification of the malarial organism and its position among the protozoa; it will be, however, scarcely worth while in a paper of this nature to enter too closely into the literature upon this point.

Laveran,(26) without definitely suggesting the biological position of the parasite, proposed the name "Oscillaria malariae" for the organism, believing that the flagellate bodies represented the more important stage. But later on,(60) wishing to hold himself aloof from any too early conclusions as to the nature of the parasite, he accepted the term "Haematozoon" used by Osler.(55) In his last publication he has accepted the classification of Metchnikoff.(59)

Osler,(55) in 1887, believed that until further studies had been made it should be classified as belonging to the genus "Haematomonas," species "Haematomonas malariae."

Metchnikoff,(59) in 1887, places the parasite in the class of Sporozoa, to which class it has been, generally, since then referred. Metchnikoff believes that the organism should be considered among the Coccidia, and proposes the name "Haematophyllum malariae." This classification has been accepted by Laveran.

Danilewsky also inclines toward this view in so far as he ranks the parasite among the Sporozoa. He proposes, however, a new group, "Haemosporidia," in which he would place these organisms as well as the similer parasites observed in birds. With this view Celli and Sanfelice (190) and Mannaberg (201) agree.

Celli and Sanfelice(190) with Kruse (164) distinguish in this subdivision, three genera:

(1). *Haemogregarina* (Danilewsky) (Frogs and Reptiles).
(2). *Haemoproteus* (Kruse) (Birds).
(3). *Plasmodium* (Marchiafava and Celli) (Man).

Kruse(261) later separates the Sporozoa into four orders:

Gregarinida.
Sarcosporidia.
Myxosporidia.
Microsporidia.

The Gregarinida he divides into the following subdivisions:

(1). *Polycystideae.*
(2). *Monocystideae.*
(3). *Coccididae.*
(4). *Haemogregarinidae.*

The Haemogregarinidae are separated into four genera:

Haemogregarina (Tortoise-Lizard).
Drepanidium (Frog).
Haemoproteus (Birds).
Plasmodium (Man).

A few authors have objected to the inclusion of these parasites among the Sporozoa. Among others, Antolisei(120) considers them to belong to the Gymnomyxa (Ray Lankester) or more exactly to the Proteomyxa, while Grassi and Feletti(122) include them among the Sarcodinia, more especially the Rhizopodia, in the division of Amoebae.

SIMILAR HAEMATOZOA IN OTHER ANIMALS.

It is scarcely worth while in this article to enter into the subject of the haematozoa of certain other cold and warm-blooded animals which so closely resemble the malarial organism. Following the earlier work of Lewis,(8) Gaule,(10, 20) Osler,* and others, extensive studies, more particularly of the blood of birds from malarial regions, have been made by Danilewsky,(44, 52, 53, &c.) Chalachnikoff,(79) Kruse,(164, 261) Celli and Sanfelice,(190) Grassi and Feletti,(205, 221) Laveran,(227, 229) Labbé(298, 310, 318) and Sacharow.(300) It has been clearly shown that birds may suffer from a malarial infection very similar to that in man.

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* Canadian Naturalist, Vol. X, No. 7.

Danilewsky (232) divides the parasites of birds into:

(*a*). The Haemocytosporon malariae, which is the cause of acute malaria; this may be seen to grow, to develop pigment, and to divide into spores just as does the malarial parasite in man.

(*b*). The parasites of chronic infection, which are represented by the Polimitus and the Laverania malariae.

He is not yet certain as to whether the parasites are the same in man and in birds, but he finds a close resemblance between the organisms of acute malarial fever in man and the Cytosporon in birds, and a similar resemblance between his Polimitus and Laverania in birds, and the flagellate and crescentic bodies in man.

Celli and Sanfelice (190) find three forms of the parasite in birds:

(*a*). A parasite with slow development which corresponds to the quartan organism in man.

(*b*). One with a more rapid development corresponding to the tertian organism in man.

(*c*). A third with the most rapid development, corresponding to the quotidian * in man. They believe, however, that the identity of the parasites of man and birds is not, as yet, established.

Grassi and Feletti (206, 231) go farther and believe that the malarial parasites of birds are the same as those seen in man; they identify in birds all the forms which they have distinguished in man. They have, however, been unable to successfully transfer organisms from man to birds or from birds to man. Inoculations from bird to bird have proven unsuccessful, excepting in a very few instances, and then only when birds of the same species were used.

Laveran (227, 229) has also made careful studies of the organisms in the blood of birds. While he recognizes the great similarity in many instances between the parasites of birds and those of the human being, he is not yet convinced that they represent the same organism.

Labbé (298, 345) divides the parasites of birds into:

(*a*). The Proteosoma Grassii; this corresponds to the Amoeba of Grassi and Feletti. Labbé describes, however, but one species.

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* At this time the Roman authors had not subdivided the aestivo-autumnal parasite into a quotidian and a tertian variety, but considered that the parasite had a cycle of development lasting about twenty-four hours.

(*b*). The Halteridium Danilewskyi (Grassi and Feletti); this corresponds to the Laverania of the Sicilian authors. Danilewsky,(186) Sacharow,(300) and Labbé,(345) all describe haematozoa which develop in the leucocytes of birds, "Leucocytozoa."

FORM IN WHICH THE PARASITE EXISTS OUTSIDE OF THE BODY. MANNER OF INFECTION.

Notwithstanding all the studies which have recently been made concerning the malarial parasite, we have, as yet, no knowledge as to the form in which it exists outside of the body, nor have we gained any positive information concerning the manner in which it enters the system.

The contagium of malaria has been supposed to enter the system in various ways; the most important points of entry which have been suggested are:

(1). The respiratory tract.
(2). The digestive tract.
(3). The skin (insect bites, etc).

(1). That infection may take place through the respiratory tract there can be little doubt, though it must be said that we have as yet no positive proof of its occurrence.

Celli and Sanfelice(190) assert that they have succeeded in transfering a malarial infection from one bird to another by intra-pulmonary inoculations. Their results, however, have been disputed by Grassi and Feletti,(221) who have been quite unable to accomplish the same thing.

Grassi and Feletti,(205) have however, found certain small amoebae in very large numbers in malarial regions. One of these, the Amoeba guttula, is readily encysted and easily carried about by the wind. This amoeba they found in the nostrils of young doves which they had placed in cages which were hung for two nights in a malarial region about two metres above the ground. In nine days these birds showed Laverania in their blood. This suggestive observation has never been repeated. More recently, Labbé(345) asserts that he has succeeded in transferring the infection by intratracheal injections of blood.

(2). Many observers still believe that the parasite is introduced chiefly through the digestive tract. Among these is Coronado.(273, 297) We have, however, no positive evidence in favor of this idea, and much against it. Celli (46) allowed six individuals to drink large quantities of water from the Pontine marshes without ill effects, while Marino (172) had similar results from like experiments.

Zeri,(153) in Baccelli's clinic, experimented in thirty cases with inhalations, drinking and enemata of water from malarious districts without a single positive result. Grassi and Feletti (205) allowed healthy individuals to drink dew collected from malarious regions without ill effects. The same observers caused healthy men to drink blood from malarial patients, and fed birds of prey on infected birds, but in no instance did they obtain positive results.

Labbé's (345) experiments with frogs and birds were also unsuccessful.

(3). Inoculation experiments have given positive proof that infection may take place through the skin, which renders more plausible the old idea that insect bites may serve to convey the contagion.

Particularly interesting in this connection are the remarkable researches of Theobald Smith,* who has shown that the haemocytozoon of Texas fever in cattle (Pyrosoma bigeminum) is conveyed from animal to animal by means of the cattle tick (Boöphilus bovis).

Experimentally, then, it has been shown that while infection through the alimentary tract is improbable, subcutaneous infection is possible, as is also intra-pulmonary infection, if we can accept Celli's and Sanfelice's and Labbé's observations on birds.

There is much room for further experimentation in this field.

RELATION OF THE PARASITES TO SOME OF THE MAIN SYMPTOMS OF MALARIAL FEVER.

(1). *The Intermittent Fever.*

Laveran,(23) in 1881, suggested that the parasites which during apyrexia remain largely in the internal organs, enter finally into the general circulation, and by an irritating influence on the nervous centres bring about the febrile paroxysm. The afebrile period, which is often so constant and regular, may represent the time which the nervous system requires to recover from the exhaustion following the paroxysm. Richard (33) believes that the rapid multiplication of the parasites produces the fever which represents the reaction of the organism against the invaders; "they" (the parasites) "excite the fever, the fever destroys them and falls in its turn;" with apyrexia the parasites multiply again.

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* "Investigations into the Nature, Causation and Prevention of Texas or Southern Cattle Fever," Theobald Smith and F. L. Kilbourne. U. S. Department of Agriculture, Bureau of Animal Industry, Bulletin No. 1, Washington, 1892.

With the more exact knowledge which we have gained concerning the cycle of development of the parasites, the coincidence of the paroxysms with the segmentation of groups of organisms has been made out.

Golgi (49) first attributed the paroxysm to the invasion of the red blood corpuscles by a new group of parasites, and asserted that the severity of the paroxysm depended on the number of fresh organisms which attacked the red corpuscles.

Antolisei (126) later called attention to the fact that it was not upon the number of new organisms which invaded the red blood corpuscles, but rather upon the number of segmenting bodies, that the paroxysms depended. Quinine given before a paroxysm may entirely prevent the development of a new group of parasites, but it cannot prevent the segmentation or the chill.

Baccelli (263) speaks of the importance of chemical poisons in producing the symptoms of malarial fever. He says that the symptoms of malarial fever depend upon, (*a*) a morphological haemodyscrasia; (*b*) a chemical haemodyscrasia. The former depends upon the progressive destruction of the red blood corpuscles by the parasites which live at their expense. The latter manifests itself in a much more intense and rapid manner, and depends upon the entrance into the circulation of as yet undetermined chemical poisons which are set free at the time of sporulation, poisons due either to the act of sporulation or to substances set free from disintegrated red blood corpuscles. These poisons are injurious to the nervous system and specially to the vasomotor ganglia; it is to their liberation that the febrile paroxysms are due. During the paroxysm many spores are destroyed, but a certain number remain to begin again their cycle of existence.

Golgi (274) in 1892, accepts this conception of the toxic origin of the fever. Plehn (262) asserts, also, that the febrile manifestations are due to the circulation of toxic substances in the blood, and makes the interesting suggestion that in some instances the febrile paroxysms occurring in individuals immediately after exposure to severe malarious influences, may be dependent upon the absorption of a quantity of these toxic substances produced by the parasite, sufficient to cause a single paroxysm. He relates two cases where individuals showing a paroxysm of this nature, developed, nine to twelve days later, characteristic malarial fever with organisms in the blood.

Mannaberg (291) likewise adheres to Bacelli's theory, which is probably accepted to-day by most observers. Strongly in favor of the idea of the toxic origin of the febrile manifestations of malaria are the observations of Brousse * and of Roque and Lemoine,(174) who have demonstrated an increased toxicity of the urine following malarial paroxysms, and of Queirolo,(108) who has shown that the same increased toxicity is observed in the sweat obtained during the paroxysm.

Even more striking evidence in favor of this view is the occurrence of the disseminated areas of necrosis in the liver described by Guarnieri,(66) Bignami,(179) and noted by Barker in another part of this fasciculus. These changes which are so characteristic of various severe infectious processes may be produced, as first shown by Welch † and Flexner, as well by soluble toxines as by actual infection.

It must be said, however, that Laveran (277) in his last work does not speak with any degree of certainty on these points. He states that toxic products may have an influence on the febrile manifestations, but that at present this is a mere hypothesis. He says "the degree of irritability of the nervous system which varies with individuals and with the date of the infection, seems to play an important role in the determination of the form and type of the fever. If the case be one of a robust individual who has the fever for the first time, the nervous system reacts vigorously against a pathogenic agent to which it is not accustomed, and one observes a continuous or at least a quotidian fever. If the patient be anaemic, reduced in strength by repeated attacks of fever, the nervous system having become less impressionable, the result is a fever with long intervals."

* Soc. de Méd. et de Chir. pratiques de Montpellier. 14 Mai, 1890. Quoted by Laveran. (229)

† The Johns Hopkins Hospital Bulletin, No. 20, March, 1892.

(2). *The Anaemia.*

Red Corpuscles.—All observers agree that the anaemia is due primarily to the actual destruction of the corpuscles by the parasites; this may be excessive. Kelsch (6) has seen as small a number of red blood corpuscles as 500,000 to the c. m. m.

A reduction in corpuscles follows each paroxysm; these reductions are more marked after the early paroxysms than in those occurring later. When a certain degree of anaemia has been reached, the losses per paroxysm are much less. When the number of corpuscles is reduced to 2,000,000, or 1,000,000, there is little tendency toward a further fall; sometimes there may be slight rises in the curve between the paroxysms—often, however, the number of corpuscles remains stationary for weeks. In pernicious cases the number of corpuscles may fall between paroxysms.

Kalindero,(92) from 400 blood counts made in fifteen cases, concludes that the number of red corpuscles is greatly diminished in malarial fever. This diminution is greater the longer the disease lasts, and the more intense the manifestations.

During the paroxysm the number of red corpuscles as well as of the white tends to increase. These changes are particularly noticeable during the first paroxysms. When, on the other hand, the anaemia is profound, the number of corpuscles tends to fall to a nearly constant number which does not appear to be modified by the paroxysm. If the paroxysms are suppressed before they have lasted long, and before the spleen is much hypertrophied, the number of red and colorless corpuscles returns to the normal.

If the fever has lasted long and the spleen is much hypertrophied, while the general condition of the patient is bad, the diminution tends to become permanent. There is no intimate relation between the enlargement of the spleen and the diminution in the number of the corpuscles.

Dionisi (173) made a careful study of the variations in the number of the red blood corpuscles during malarial fever with the following results:

(1). In aestivo-autumnal fever, the reduction in the number of red blood corpuscles bears a direct relation to the number of organisms.

Where the parasites are numerous there is a constant reduction of from 200,000 to 1,000,000 with each febrile paroxysm; where the parasites are scanty the reduction is less.

(2). When crescentic bodies are present in addition to the other forms, they seem to exert no influence on the blood changes.

(3). When, after a paroxysm, the number of corpuscles has suffered a sudden and very marked diminution, the succeeding paroxysms may be followed by but a slight reduction only or even by an increase.

(4). In relapses the reduction per paroxysm is less than in a primary infection.

(5). In infections determined by the amoeboid forms (acute aestivo-autumnal infection) there is, during apyrexia, no complete return of the red corpuscles to their normal number. Some attempts at restitution may be seen during the first several days of apyrexia, while after this, during perhaps eight to fifteen days, there may be a steady reduction of from 1- to 500,000 red blood corpuscles without the appearance of any parasites in the blood.

(6). Only after marked and continuous reductions following each paroxysm does there occur in the afebrile period a relative restitution of the red blood corpuscles; this may be slow or rapid.

(7). If the increase in the corpuscles has begun, the presence of crescents has no deleterious effect.

(8). In tertian and quartan fevers the same changes are observed, excepting that in the afebrile period there is a rapid and almost complete restitution of the red blood corpuscles.

(9). The colorless corpuscles follow the same course as the red, both in apyrexia and fever. In later periods, however, when the red corpuscles have increased, there may still be a marked diminution in the colorless elements.

Bastianelli (246) noted the association of the anaemia of cachetics with actual changes in the marrow produced by the infection.

Bignami and Dionisi (332) distinguish four types of post-malarial anaemia:

(1). Anaemiae in which the examination of the blood shows alterations similar to those observed in secondary anaemiae, from which they differ only in that the leucocytes are diminished in number. The greater part of these cases go on to recovery; a few, without any further change in the haematological condition, pursue a fatal course.

(2). Anaemiae in which the examination of the blood shows alterations similar to those seen in pernicious anaemia—presence of gigantoblasts. These cases end fatally.

(3) Anaemiae which are progressive, as a result of the lack of compensation by the marrow for losses brought about by the infection. At autopsy the marrow of the long bones is found to be wholly yellow, while the marrow of the flat bones is also poor in nucleated red corpuscles.

(4). Chronic anaemiae of the cachectic, which differ from the above mentioned types by clinical and anatomical characters in that the special symptoms of malarial cachexia prevail, while one observes post-mortem, a sort of sclerosis of the bone marrow. The marrow of the long bones is red and of an increased consistency; the giant cells are very numerous and many are necrotic; the nucleated red blood corpuscles are very rare, and the colorless polymorphonuclear * corpuscles are present in small numbers.

Colorless Corpuscles.—Kelsch(7) noted that the leucocytes were diminished during the paroxysm more than the red blood corpuscles, an absolute diminution sometimes to one-half or one-third the normal number. From this they may show a slight increase just at the beginning of the paroxysm. Usually the number of leucocytes returns to normal much more slowly than that of the red corpuscles.

The minimum of the leucocytes corresponds to the maximum of the splenic enlargement. In cachexiae with chronic splenic tumor he found, generally, a diminution in the number of leucocytes, though in some pernicious cases there was a leucocytosis.

Hayem † noted the absence of increase in the colorless corpuscles.

Kalindero(92) noted a marked diminution in the number of the leucocytes, especially in the more acute cases. During the paroxysm there is a tendency toward an increase in the number.

Dionisi,(173) as has been stated, noted that the colorless corpuscles show the same variations in number as do the red, excepting that in some long continued anaemiae the white corpuscles remain subnormal in number for a longer time.

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* This term first used by Cabot (Boston Med. and Surg. Journal, March 20, 1894), a translation of the German term "Polymorphkernige" appears to me the best which we have in English.

† Le Sang, Paris, 8°, 1889.

Pée* remarked the absence of any leucocytosis in intermittent fever.

Bastianelli (346) noted also a diminution in the number of leucocytes during the attacks; this he thought might depend on the active phagocytosis with subsequent necrosis. He noted colorless elements in karyokinesis in the spleen and sometimes in the circulating blood—a regenerative process, he believed, to compensate for the active destruction which had occurred. He made a series of differential blood counts in specimens stained according to Ehrlich's methods, showing that in these cases with a diminished number of leucocytes the relative proportion of the small mononuclear elements remained normal, while that of the large mononuclear leucocytes was much increased, and the polymorphonuclear neutrophiles appreciably diminished; eosinophilic cells were generally scanty in number.

The striking similarity of these counts to the condition seen in typhoid fever will be noted.

Billings,(338) in this clinic, made a series of observations confirming, in the main, these results. He notes that the leucocytes, which are generally sub-normal in number, show a slight increase at the beginning of the febrile paroxysm. Following this increase there is a rapid diminution continuing throughout the paroxysm. The smallest number of leucocytes is seen at the end of the paroxysm when the temperature is sub-normal. From this time the number shows a gradual slight increase, which, as has been said, is slightly accentuated just at the beginning of the paroxysm. The changes in the relative proportion of the different varieties of leucocytes he found to be just as noted by Bastianelli. In four cases of post-malarial anaemia, Billings found quite a marked leucocytosis.

Haemoglobin.—Rossoni (106) studied the variations in the percentage of haemoglobin in association with blood counts, and arrives at the following conclusions:

(1). No acute infection results in as active a deglobulization as does malarial fever.

(2). In all cases of malarial fever there is an immediate diminution in the number of corpuscles and the amount of haemoglobin. This loss generally bears a direct relation to the duration of the infection. In pernicious cases, however, a diminution of as much as two-thirds of the total amount may take place in from one to three days.

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* Diss., Berlin, 1890.

(3). The gravity of pernicious cases does not always bear a direct relation to the extent of the loss in haemoglobin.

(4). The destruction of haemoglobin and corpuscles bears, generally, a direct relation to the number of parasites in the blood. Occasionally, however, cases with high fever and marked losses in haemoglobin and corpuscles, may show but few parasites in the circulating blood. A long-continued diminution of haemoglobin is often associated with the presence of crescents.

(5). The loss in haemoglobin and corpuscles is rarely evident during the paroxysm, but begins with apyrexia and may continue for several days afterwards.

(6). Recovery from malarial anaemia is slower than from the other acute anaemiae.

(7). Usually the haemoglobin and corpuscles are equally diminished, but sometimes the haemoglobin is reduced disproportionately.

(8). The rapid diminution in haemoglobin is sometimes a valuable point in differential diagnosis between malarial fever and enteric fever or pneumonia.

(9). The restitution of the haemoglobin in malarial anaemia is often incomplete, and individuals living in malarious districts have often a slightly smaller percentage of haemoglobin than those living elsewhere.

(3). *Other Symptoms.*

The pathogenesis of a number of the other important symptoms of malarial fever has been much elucidated by the knowledge we have gained concerning the parasites.

The *coma* in some pernicious cases has been shown by many observers to be associated with enormous collections of malarial parasites and pigment in the cerebral capillaries. The parasites may be free and are often in the process of segmentation; they may be contained in red corpuscles; they may form actual thromboses. The endothelial cells of the capillaries are often swollen and degenerated, while in many places perivascular punctate haemorrhages may be seen. These so-called "pigment thromboses" were first noted as long ago as 1854, by Planer (4) who attributed to them the comatose symptoms.

In one case of pernicious fever with symptoms of *bulbar paralysis* Marchiafava (167) demonstrated the special localization of similar changes in the region of the bulbar nuclei.

While these local conditions may be reasonably supposed to account for many of the cerebral symptoms in pernicious fever, it must be acknowledged that we cannot deny a possible toxic cause for some. It is also interesting to note the hypothesis of Guarnieri,(66) who, finding enormous accumulations of large macrophages blocking many intralobular capillaries in the liver, and extensive areas of necrosis, called attention to the similarity between the cerebral symptoms in these cases and those produced artificially in animals by ligature of the portal vein.

In cases with *choleriform symptoms*, enormous accumulations of the parasites have been noted in the gastro-intestinal mucosa, producing marked secondary changes. Marchiafava (330) has recently devoted a paper to this point.

MELANIFEROUS LEUCOCYTES—PHAGOCYTOSIS—SPONTANEOUS RECOVERY.

The presence of melaniferous leucocytes in the blood of patients suffering with malarial fever has, as has already been said, been known for years. Laveran,(29, 60) in his earlier articles, noted their appearance, especially during and just after paroxysms. Marchiafava and Celli (61) early noted that they might contain the red blood corpuscle as well as the pigment and parasite. Golgi,(49) in his first article on the quartan organism, noted that phagocytosis was most marked during the paroxysm, from its height on to the period of apyrexia, the leucocytes taking up the pigment left free by the sporulating forms.

Metchnikoff (59) lays much stress on phagocytosis as an active protective process. The malarial organisms are engulfed and destroyed particularly by the macrophages of the spleen and liver, and to a lesser extent, by the ordinary leucocytes.

Guarnieri (66) asserts that the process has one of its most important seats in the capillaries of the liver, the slow current and the relatively large size of the vessels affording a particularly good opportunity for the engulfing of the parasites by the macrophages. The endothelial cells of the capillaries have also a phagocytic action.

Golgi,(78) in 1888, devotes a special study to the phagocytosis in the tertian and quartan fevers. In these fevers phagocytosis takes place periodically as a regular function of the leucocytes. This process occurs in connection with certain distinct phases in the cycle of existence of the parasite, and at a regular period in each paroxysm. In fresh blood one first notices phagocytosis with the beginning of the paroxysm; the process becomes more marked several hours later, and ends several hours after the paroxysm, lasting altogether from eight to twelve hours. At the beginning of the attack, the leucocytes contain either the whole segmenting forms, fragmenting bodies, or the free pigment blocks left after segmentation. The simple pigment-bearing forms are the commonest. Toward the end of the paroxysm the forms containing the whole parasite are rare, probably because the engulfed bodies have been digested leaving only the fine granules. Punctures of the spleen show that a much more active phagocytosis is carried on there than in the circulating blood. Golgi believes that all this supports Metchnikoff's theories of phagocytosis; he inclines to believe that it is largely through the action of the phagocytes that any given attack of malarial fever is prevented from becoming pernicious, though he acknowledges that it remains to be definitely proven that the parasites which are taken up are at the height of their functional activity, and not forms which are already of somewhat diminished vitality.

Bignami(179) in 1890 in his studies of the pathological anatomy of pernicious fever, describes the extensive phagocytosis which takes place in the spleen, liver, and bone marrow, and notes also the fact that the phagocytes may contain not only whole parasites but the red corpuscles, usually degenerated, in which the organism may lie. He is inclined to ascribe considerable importance to phagocytosis as a protective process. He notes, however, degenerative changes in some large macrophages—loss of the staining power of the nucleus, fragmentation of the nucleus—and suggests the possibility that in these instances spores which have been taken up may preserve their vitality and later, after the death of their host, escape and become the cause of a relapse.

While these observers rather incline to regard the phagocytosis in the sense of Metchnikoff, as an active warfare against the parasites, other observers take a rather more sceptical view.

Osler,(91) in 1889, believes that we have, as yet, insufficient evidence to prove an aggressive warfare of the part of the leucocytes against the malarial parasites.

Bastianelli,(246) in 1892, published an elaborate study of the leucocytes in malarial infection. He confirms Golgi's observations concerning the phagocytosis in tertian and quartan fevers, and devotes himself especially to the aestivo-autumnal fevers. Here, as in the regularly intermittent fevers, there are indications of a periodicity in the phagocytosis, but this periodicity is by no means as well marked. The pigmented leucocytes are more numerous at the time of sporulation, beginning to appear with the paroxysm, and increasing to a maximum at the precritical elevation (malignant tertian fever), during the crisis, or in the first hours of apyrexia. At the beginning of the attack, owing to the small number of parasites in the circulating blood, the pigmented leucocytes may be the chief evidence of the malarial nature of the process. These phagocytes may not, however, disappear during apyrexia, owing, in part, to the great frequency of the shrunken and brassy colored red corpuscles which are readily taken up. Again, owing to the irregularity and multiplicity of the paroxysms, phagocytes dating from a former access are often present at the beginning of a second.

Sometimes the number of phagocytes is enormous. In the milder cases one sees only a few ordinary leucocytes with pigment granules, and a few macrophages containing blood corpuscles as well as parasites. These latter forms are much more frequent in severe infections; they may show various degenerative changes in their protoplasm. Large endothelial cells containing pigment and parasites may also be seen. These often show degenerative changes. The following, in order of frequency, are the bodies which are more commonly found included in phagocytes: (*a*) pigment; (*b*) sporulating forms and spores; (*c*) red corpuscles, normal or decolorized, containing sporulating forms or bodies with central pigment clumps; (*d*) red corpuscles, decolorized or brassy colored and shrunken, containing parasites; (*e*) free bodies with central pigment clumps; (*f*) more rarely red corpuscles of normal appearance containing parasites in the amoeboid stage, or free amoeboid bodies; (*g*) crescentic bodies. Sometimes one may see entire phagocytes engulfed by macrophages. The phagocytes themselves often become necrotic, showing vacuolic and fatty degeneration of their protoplasm, and fragmentation or loss of affinity for coloring matters in the nucleus. "The phagocytic action of the leucocytes occurs at all moments in the life of the parasite in this class of fevers, as well in the pyrogenic as in the non-pyrogenic* cycle: it occurs whenever parasites or pigment become free, or when the red corpuscles are profoundly altered (necrosis with brassy color, decolorization). Therefore one cannot say absolutely that the phenomena of phagocytosis are associated with a definite phase of the cycle of evolution of the parasite."

With this the observations of Marchiafava and Bignami(245) agree. Bastianelli disputes Golgi's assumption that the phagocytosis is the chief element which prevents the ordinary tertian and quartan infections from becoming malignant. In cases of spontaneous cure there is no particular increase in the phagocytosis—rather the opposite.

In the severe cases, on the other hand, there is no evidence of a lack of activity on the part of the phagocytes; indeed, the process here is much more active; it is not upon the absence of phagocytosis that the severity of a paroxysm depends, but rather upon the amount of toxic material which is set free in the circulation. It is not evidence of increased phagocytosis which one observes in the cases of spontaneous recovery, but rather an increased number of fragmenting and degenerating parasites—parasites the vitality of which has been injured by some other cause (Celli, Bastianelli and Bignami, Antolisei). Furthermore, Bastianelli notes the rhythmic course which untreated malarial infections often pursue; a gradual increase in the severity of the paroxysms; a period of oscillation; a spontaneous recovery; a relapse after one or two weeks, which pursues the same course, and so forth. It is difficult to see why, if phagocytosis alone be the cause of these spontaneous cures or rather arrests, they should always occur after a certain number of paroxysms and not at the beginning of the infection. It would seem more probable that after a certain time some other factor comes into play which diminishes the vitality of the parasites and makes them an easy prey for the phagocytes. The important element in spontaneous recovery is the oscillation in the virulence of the parasite and not the phagocytosis. The parasite may die in the blood current without the intervention of the phagocyte. "If, however, the phagocyte is not the preponderant factor in determining the course of the infection, it maintains always a most important position in malarial processes; its constant action is exercised in eliminating a large number of pathogenic elements and in facilitating the return of the organism to its normal functions by freeing it from all extraneous injurious substances." With Bignami, he agrees in suspecting the possibility that some spores may remain living in the macrophages of the spleen, liver, and bone marrow, whence they may later escape, causing a relapse.

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* Crescentic and ovoid forms (?) (W. S. T.).

Mannaberg (201) asserts that the febrile paroxysm, either from the high temperature or from the circulating pyrogenic substance, exerts an injurious action on both the half- and full-grown parasites. He concludes: "The spontaneous cure of malaria depends upon three factors, namely: the activity of the macrophages of the spleen and the bone marrow (to a lesser extent of the endothelial cells of the cerebral vessels); on the circumstance that numerous parasites remain sterile; finally, on the destructive action of the febrile paroxysm which is manifested by the fragmentation of numerous half- and full-grown parasites."

ACTION OF QUININE.

The specific action of quinine in malarial fever cannot be discussed here. Its direct action on the parasite has, however, been studied of late with interesting results.

As long ago as 1867, Binz * concluded that the efficacy of quinine in paludism depended upon its action as a protoplasmic poison on some lower organism which he assumed to be the cause of the process.

Laveran,(23) in 1881, asserted that "it is because it destroys the parasite that quinine causes the disappearance of the manifestations of paludism," a statement which has received abundant confirmation since. He showed that by allowing a 1–10,000 solution of quinine to run under the cover glass, the movements of the parasite were immediately arrested.

Marchiafava and Celli (45) showed that the same results could be obtained by using an 0.5 or 0.75 per cent. salt (NaCl) solution, and also with distilled water or Pacini's solution, while Grassi and

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* Centralblatt für die Med. Wiss., 1867, p. 308.

Feletti(281) showed that after shaking malarial blood with distilled water for an hour, inoculation experiments remained negative.

Binz,(323) however, asserts that these latter experiments are no evidence that quinine does not act in this manner, as both salt and distilled water are protoplasmic poisons.

Rosin(311) alone, on testing the action of 1–5000 solutions of quinine on the tertian parasite, found active movements of the pigment granules forty-eight hours afterwards.

Further proof as to the manner of the action of quinine on the parasites has been obtained by a study of the organisms found in the circulating blood after its administration.

Golgi(274) studied the action of quinine on the tertian and quartan organisms. The quartan parasite in its endoglobular stage shows a coarser granulation with a metallic reflex, while the protoplasm shows a certain cloudiness; at times one may see abortive segmenting forms which are smaller than the normal, with a lack of regularity and fewer segments; the pigment, also, may not collect as sharply in a clump in the middle of the parasite. In the tertian parasite the changes are more marked, owing to the greater normal activity of the organism. The body is round and immovable, and shows a sharper outline than usual, while the pigment has a peculiar metallic reflex and tends to collect in clumps. Full grown tertian forms may show the large transparent swollen condition with very active movements of the pigment. Sometimes the pigment collects toward the periphery and a hyaline space is left in the middle.

Mannaberg(291) asserts that three hours after the administration of 0.5 of quinine the amoeboid forms of the tertian parasite show a marked diminution in their activity. In several hours more the number has greatly diminished, while many of those present are fragmented ("zerrissen"), so that they form several separate spherules in the red corpuscle. The full grown forms show a cessation of the movements of the pigment, the body showing a somewhat refractive homogeneous appearance. The large hydropic forms with active pigment may also be seen. Both of these forms, according to Golgi and Mannaberg, may be seen normally during the paroxysm; they are probably degenerate forms. The segmenting forms are sometimes imperfect.

Baccelli(263) noted that in aestivo-autumnal fever there was at first after quinine, an increase in the activity of the small amoeboid forms which shortly—often in twenty-four hours—disappeared without showing any outward signs of degeneration.

Marchiafava and Bignami(245) also studying the aestivo-autumnal fevers, note that the administration of quinine is followed by an increase in the number of shrunken, brassy colored corpuscles; they believe that the included parasites are incapable of further development.

More direct proof of the destructive action of quinine on the malarial parasite is offered by the researches with stained specimens by Romanowsky(201, 210) and Mannaberg.(203, 291) Both of these observers note the loss of staining properties in the chromatin substance of the nucleus. They note also that in the sporulating forms, after quinine has been given, the greater part of the segments show no nucleolus. These changes in the nucleus they believe to be evidence of a necrotic process; the spores without nucleolus Mannaberg terms "still-born." Romanowsky studied the tertian parasite; Mannaberg both tertian and quartan.

All observers agree that the crescentic bodies are affected slowly, if at all, by quinine.

Golgi(274) asserts that in tertian and quartan fever quinine acts most markedly on the young free spores, less upon the more advanced forms where the red corpuscle is in greater part destroyed, and least upon the young endoglobular forms.

If quinine be given several hours before a paroxysm it will not prevent segmentation, but it destroys the new group of organisms—the fresh segments. Segmentation taking place and toxic substances escaping, the chill occurs, being at most a little modified and retarded; further development of this group of organisms is, however, cut off.

This, then, is, according to Golgi, the best time to administer the drug, though continued doses may be needed to wholly eradicate the infection. By giving single doses in this manner a double tertian infection, or a double or triple quartan may be changed at will into a single tertian in the one instance, or into a single or double quartan in the other (vide page 113).

Marchiafava and Bignami,(245) studying the aestivo-autumnal parasite, conclude that "the maximum and most rapid action of the remedy is exercised on that phase of the extraglobular life of the parasite which follows the completed segmentation." They note, as does Golgi, that the segmentation cannot be prevented if quinine be given when the parasite has reached the preparatory stages. "Quinine acts on the amoeba of malaria," they say, "during those phases of its life in which it absorbs nourishment and develops; when the nutritive activity comes to an end, the transformation of haemoglobin into black pigment being accomplished, and the phase of reproduction begins, then quinine becomes inefficacious against this process." They agree with Golgi that to best combat the development of the infection, quinine should be in solution in the blood at the time of the setting free of the spores: *i. e.*, it should be given several hours before the paroxysm.

III.—GENERAL ANALYSIS OF 616 CASES OF MALARIAL FEVER.

During the period between June 14th, 1889, and January 1st, 1894, 616 cases of malarial fever were observed in the wards and at the out-patient department of the Johns Hopkins Hospital. Of these, 333 were treated in the wards of the hospital, while 283 were treated at the out-patient department. Relapses of cases occurring in the hospital, treated later in the out-patient department, have not been counted in the list. Two of the 333 cases treated in the hospital were relapses of cases already on the list, and have therefore been left out in some of the tables.*

AGE.

Of 614 cases in which the ages were obtained, there were:

Between 1 and 10 years of age	18
" 10 " 20 " " "	146
" 20 " 30 " " "	204
" 30 " 40 " " "	130
" 40 " 50 " " "	65
" 50 " 60 " " "	36
" 60 " 70 " " "	11
" 70 " 80 " " "	8
" 80 " 90 " " "	1
Total	614

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* Relapses of cases treated in the out-patient department are not counted as new cases.

Below is a table with the ages of 614 patients selected at random from the admissions to the hospital and the out-patient department—331 from the hospital, and 283 from the dispensary.

Between 1 and 10 years of age	14
" 10 " 20 " " "	92
" 20 " 30 " " "	207
" 30 " 40 " " "	114
" 40 " 50 " " "	84
" 50 " 60 " " "	59
" 60 " 70 " " "	33
" 70 " 80 " " "	11
" 80 " 90 " " "	0
Total	614*

A comparison of these two tables shows clearly the greater frequency of malarial fever among children and young adults. This is probably due not so much to a greater susceptibility as to the fact that the young adult is more exposed to malarial influences—remaining out of doors in malarial districts at night, etc.

SEX.

Of these 614 patients there were—males, 493; females, 121. A table of 614 admissions to the hospital and out-patient department for the same time shows males 396; females 218. The differences in the number of women depends, probably, largely on the fact that the men are so much more likely to be employed in malarious districts: boating on the bay; farming; fishing; while the women, remaining in the house, are spared.

RACE.

Of these patients there were: white, 585; colored, 29, or 4.7 per cent. In the hospital and dispensary, taking the cases at random, there were: white, 539; colored, 75, or 12.2 per cent. These figures would tend to uphold the generally accepted view that the negro is relatively insusceptible to malarial infection.

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* As there is no children's ward in the hospital, while the cases treated in the children's room at the out-patient department did not come under our observation, the statistics as regards children under ten years of age are of no value.

RELATION OF THE CASES TO THE TIME OF YEAR.

The following table shows the relation of the occurrence of these cases to the various months of the year.

Jan.	Feb.	Mar.	Apr.	May.	June.	July.	Aug.	Sept.	Oct.	Nov.	Dec.	Total.
12	8	18	28	35	33	74	67	129	137	45	28	614

From this table it appears that while in the winter months, December, January, February, and March, malarial fever is at a minimum, with the month of April the number of cases begins to increase, as a general thing, showing a gradual steady rise until the climax which occurs in the months of September and October. In November and December, a well-marked fall begins. This table, while it gives a good general idea of the distribution of the malarial infection throughout the year, is, however, a trifle misleading if taken too strictly. The cases during the latter half of the year 1889 were few, as the hospital was new and the clinics had not yet developed, while the cases from January to August of 1894 represent a much larger clinic. The proportion of cases occurring in the first seven months is thus over-represented, while the second half-year suffers, the under-representation of the cases in August being especially marked. The following table, dealing with the cases during the four years from January 1st, 1890, to January 1st, 1894, gives a more accurate representation of the variation of malarial fever with the seasons:

Jan.	Feb.	Mar.	Apr.	May.	June.	July.	Aug.	Sept.	Oct.	Nov.	Dec.	Total.
9	8	8	17	21	18	38	66	122	120	38	25	490

It may thus be seen that more than five-sixths of the cases of malaria observed by us occur in the second half-year; nearly one-half occur in the months of September and October.

It has seemed to us, however, a matter of interest to make another table, which appears below, showing the time at which the patient observed the first symptoms of the affection; this shows several interesting variations from the other tables:

Jan.	Feb.	Mar.	Apr.	May.	June.	July.	Aug.	Sep.	Oct.	Nov.	Dec.	Not Stated.	Total.
8	2	21	21	44	23	83	103	156	69	16	8	60	614

We see thus that the smallest number of cases occurred in the months of December, January, and February, only two cases beginning during the month of February. From this time on there is a fairly steady increase until the month of May which shows the spring maximum. In July again an increase begins, reaching the climax in September, when 156, or more than one-fourth of all the cases, appear to have shown their first symptoms; 103 cases originated apparently in August, while only 69 appear to have originated in October; in 60 cases the date of onset could not be obtained. Thus, nearly one-half of all the cases originated in the months of August and September, and whereas 137 cases were first admitted to treatment in October, only 68 dated their symptoms from that time.

Of these 616 cases, there were:

Primary attacks	396
Relapses or new infections	166
Uncertain	52
Relapses of cases already classified	2

GENERAL SUMMARY OF SOME OF THE MORE IMPORTANT SYMPTOMS AND COMPLICATIONS.

The following tables deal with some of the more important symptoms noted in these 616 cases taken *en masse* without regard to type.

Chills.—There were:

Chills in	479	cases.
Chilly sensations in	41	"
Vague symptoms of headache, anorexia, muscular pains, etc., in	90	"
No history in	6	"

Vomiting.—Vomiting was noted in 84 cases, though it is probable that it occurred in many more.

Epistaxis occurred in 19 instances.

Condition of the Bowels:

Diarrhœa occurred in	80	cases.
Constipation occurred in	161	"
Alternate diarrhœa and constipation	5	"
The bowels were regular in	157	"
No note was made in	213	"

Urine.—The analysis of the urine in the 335 cases occurring in the hospital shows the following results:

The urine was normal in	151	instances.
Albumin was noted in	133	"
Casts of the renal tubules were found in	31	"
The diazo reaction was present in	18	"
Acute haemorrhagic nephritis was present in	3	"
Severe subacute diffuse nephritis was present in	1	"
No note was made in	51	"

In not a single instance of malarial fever observed in the hospital or in the out-patient department, was haematuria present, with the exception of the three cases of acute nephritis, where the blood was present merely in the shape of altered red corpuscles, giving a smoky color to the urine.

Condition of the Blood.—In 94 cases pallor was noted; in 21 cases there was grave anaemia.

Cutaneous manifestations.—In 61 cases, *herpes labialis* was noted; in 3, a *petechial* eruption; in 3 instances an eruption suggesting the *rose spots* of typhoid fever was found; in one case, general *erythema;* in one, a rash resembling *measles;* in one, *eczema;* in one, a *varioliform eruption; urticaria* was present during the paroxysm in 3 cases; *herpes zoster* was present in one case.

Respiratory Organs.—In 16 cases, *bronchitis* was noted, while in a number of others a slight cough, without physical signs, was present.

Complications.—Among the chief complications, the following may be mentioned:

Chronic valvular disease of the heart	5
Arterio-sclerosis	1
Pregnancy	2
Secondary syphilis	3
Congenital syphilis	1
Incontinence of urine	1
Epilepsy	2
Pleurisy	2
Pneumonia	2
Asthma	1
Cancer of the uterus	1
Cancer of the jaw	1
Subacute rheumatism	1
Tonsillitis	1

Amoebic dysentery	1
Entero colitis	2
Typhoid fever	1
Chronic nephritis	1
Acute nephritis	2
Anasarca	1
Keratitis	1
Furunculosis	1
Parotitis	1
Adenitis	1
Acute mania	1
Alcoholism	1

Cases of Pneumonia associated with Malarial Fever.—Two cases of malarial fever in the hospital were complicated by pneumonia.

CASE 9424.—C. J., aged 30, a laborer, native of the United States, admitted March 16th, 1894, complaining of loss of appetite and cough. Family and personal history bear no relation to his present trouble, excepting for the fact that he had malarial fever a year ago; chills at uncertain intervals. He has been living recently in a very malarious district. The mistress of the house in which he lives and her three children are all suffering from chills and fever at present. For several weeks, has not been feeling well; appetite poor; has been languid and easily tired; gave up work three weeks ago.

Two days ago the patient began to complain of a very severe headache, nausea and vomiting, and thinks that he has had fever since this time; no chills; diarrhoea, three or four movements daily; slight cough for several weeks.

Hasty examination of the *blood* on admission showed no malarial organisms. *Urine* normal, yellow, cloudy, acid, 1020, trace of albumen, distinct diazo reaction, no sugar nor bile; microscopically, leucocytes and epithelial cells; one doubtful granular cast.

The temperature on admission was 102°, reached 105.2° at 10 p. m., and was 101.8° at 8 a. m. the next morning.

17–3–94. Patient was in bed; well nourished; tongue coated; pulse, twenty-five to the quarter, regular in force and rhythm; heart and lungs negative; abdomen negative, excepting for an increased area of splenic dulness.

At 10.30 a. m. the blood showed half- and full-grown malarial organisms of the tertian type with fine, dancing, brownish pigment; one intracellular hyaline body; one early segmenting form. Temperature steadily elevated.

At 4 p. m. no malarial organisms seen in two slides. Leucocytes, 10.000.

18–3–94. "Last night the patient complained of pain in the right axilla—a "stitch"; respiration at the right base appeared somewhat enfeebled, and the resonance was slightly impaired. Though the malarial organisms were few in number, the patient was ordered quinine, gr. x (0.65), at nine and twelve, and gr. v (0.32), every four hours afterwards. Patient passed a restless night, the temperature this morning being 102.3°. Pulse is rapid, over 130, rather soft." Well marked evidences of consolidation were found at the right base.

Leucocytes at 10 a. m., 14,500; at 4 p. m., 17,000. From this time on, the patient went through a very serious attack of pneumonia, the temperature falling by lysis. The quinine was continued only three days, gr. lxxxv (5.32) in all. The temperature reached the normal on the 26th of March. No malarial organisms were seen after the 17th.

On the afternoon of the 9th of April, the patient complained of having a headache, and the temperature was found to be 103.6°. It fell at midnight to 99.2°. On the 10th, the temperature rose between 12 and 4 p. m. to 103.8°, falling gradually to 99.2° at 8 a. m. on the following morning. Examination of the blood on the 10th showed tertian parasites. Quinine, gr. v (0.325), three times a day, was ordered; the patient made an uninterrupted recovery.

This case is of interest in that it is the only one which has occurred, since the opening of the hospital, where malarial organisms were found in the blood during the actual existence of a pneumonia. It is in every way probable that the patient had had for a week or two a tertian infection which had not yet reached a sufficient intensity to produce actual chills; that during this time the pneumonia also developed. During the convalescence, twenty days after the omission of quinine, a relapse of the tertian fever occurred. So far as could be made out, the presence of the malarial infection caused no essential modification of the chart of the pneumonia.

Case 9963.—W. B., aged seven, admitted on May 24th with single tertian malarial fever, though indications of a second group of organisms were present. As the chart shows, the patient had an abortive paroxysm on the 26th, the temperature remaining normal afterwards until the 30th. Quinine was given on the 26th, and no malarial organisms were seen afterwards.

On the 30th the patient had a chill at 4 a. m., associated with some vomiting. The blood showed a slight leucocytosis. The temperature remained continuously elevated until the 3rd of June. Nothing could be made out on physical examination until the 2nd of June, when evidences of consolidation at the right apex appeared. Crisis on the evening of the 3rd. Quinine was discontinued on the 1st of June. On the 18th of June the patient had a chill, temperature rising at 1.30 p. m. to 103.8°, blood showing one group of organisms. Quinine was begun on the 19th. A few fragmented, extra-cellular bodies were seen on the 20th, when the patient was discharged with a prescription for quinine, the temperature having remained normal.

In this case it will be seen that the pneumonia developed during the malarial infection which was never quite eradicated, a relapse occurring twenty-three days after the last organisms had been seen. In neither of these instances did the pneumonia show anything remarkable in its course, nor is it likely that the malaria exerted any influence upon the pneumococcus infection, excepting in so far as it may have prepared the soil.

Case of Typhoid Fever combined with Malarial Fever.—In one instance malarial fever was associated with typhoid fever.

The patient, J. D., aged 20, Irish, was admitted on the 16th of October, 1891, complaining of chills, fever, headache, cough, and occasional bleeding from the nose.

The temperature on admission, was 100°; it fell on the morning of the 17th to 96°. The *blood* on the 17th showed fairly numerous, non-pigmented, intracellular, hyaline bodies. Physical examination was negative. On the 17th, as the chart will show, the patient had a chill, the temperature remaining elevated for nearly twelve hours. During the next several days, there were slight oscillations in the temperature, which remained nearly normal. Quinine, 0 26 three times a day, was ordered on the 17th. The last malarial organism seen in the blood was an ovoid body, with coarse pigment granules, which was seen on the 23d. The temperature began to rise on the 22d, reaching 104.8° at 4 p. m. on the 23d, the patient passing through a long, severe attack of typhoid fever. Quinine was omitted on the 26th.

The patient made a good recovery, leaving the hospital on the 19th of January. No malarial organisms nor symptoms of malarial fever were noted.

In this instance, the typhoid fever unquestionably developed during the course of a malarial infection, organisms still being present in the blood at the beginning of the rise of temperature. The case demonstrates the possibility of the co-existence of the two affections.

IV.—THE VARIETIES OF THE HAEMATOZOA OBSERVED IN THE MALARIAL FEVERS OF BALTIMORE.

Methods of Examination of the Blood.

Almost all the examinations of the blood upon which this article is based, were made with fresh specimens. In a number of instances we have used different staining methods, but the examination of the fresh blood, when carefully carried out, has always seemed to us simpler and more satisfactory. The steps toward the preparation of the specimen are simple, but certain precautions must be rigidly adhered to. The cover glasses and the slides must be carefully washed in alcohol, or alcohol and ether, in order to remove all fatty substances. They should always be washed immediately before use. The blood may be taken from any part of the patient's body, though in our practice we prefer the lobe of the ear, inasmuch as it is less sensitive and more easily approached than the finger tip, while a smaller puncture will draw more blood. This method is also more satisfactory than the puncture of the finger in that the patient cannot so readily observe the proceeding, a point of considerable importance in nervous patients and children. The ear is at first thoroughly cleaned; the lobe is then punctured with a small knife or lancet. The first several drops of blood are wiped away. The freshly cleaned cover glass is then taken in a pair of forceps and allowed to touch the tip of a minute drop of blood; it is then placed immediately upon the perfectly clean slide. It is well, if a third person be present, to allow the slide to be vigorously rubbed with a clean linen cloth just before the application of the glass. The spreading out of the drop of blood will thus be considerably facilitated. If the slide and the cover are perfectly clean, the blood will immediately spread out between them, and unless the drop of blood has been too large, the corpuscles may be seen lying side by side, entirely unaltered in their main characteristics. The drop of blood which is taken should be very small, unless the patient is very anaemic, and care should also be exercised that the tip of the drop only should touch the cover. If the cover be placed rudely against the drop, and pressed, perhaps, also against the ear, the blood may so far spread out that the process of drying may have begun before the glass is laid upon the slide. If this be the case, the immediate spreading out of the blood between the slide and the cover does not occur. No pressure whatever should be exerted upon the cover which should not be pushed or allowed to slide. We have not, in our examinations, used the prepared slides of Hayem, nor have we endeavored to preserve our specimens for a longer time by the application of vaseline or paraffine about the cover glass. The specimens will remain in good condition for a considerable length of time, an hour or more, long enough to be thoroughly examined. For the examination of fresh blood, a good oil-emersion lens is almost necessary. It should not be forgotten, however, that in the absence of such optical assistance, we may yet study the organisms with some satisfaction, for Laveran made his discovery and the majority of his researches with ordinary dry lenses of moderate power. As has been said, however, for satisfactory work a $\frac{1}{12}$ oil-immersion lens, with a 4 eye-piece, is advisable, and, indeed, if the lens be good, eye-pieces as high as 8, or even more, give satisfaction.

For the preparation of permanent and stained specimens, we have had best results with eosin and methylene blue. In the preparation of these specimens we rather prefer fixing by means of absolute alcohol, or absolute alcohol and ether, to the methods of heating. A specimen hardened for half an hour in absolute alcohol and ether, may be stained with a concentrated aqueous solution of methylene blue for from half a minute to a minute with excellent results.

A good contrast stain may be obtained by the following method: The specimens are placed for thirty minutes in absolute alcohol and ether, dried, and stained for from thirty seconds to five minutes in a ½ per cent. solution of eosin in 60 per cent. alcohol, washed in water, dried, and placed for from thirty seconds to a minute in a concentrated aqueous solution of methylene blue, washed, dried between filter paper, and mounted in Canada balsam. The methylene blue stain may not be very intense, but at times beautiful pictures may be obtained.

The most satisfactory results which we have obtained have been with a modification of Romanowsky's method. Romanowsky's (210) (vide p. 43) directions are carried out strictly, excepting that the specimens, instead of being fixed by heat, are placed for from ten to twenty minutes in absolute alcohol. By this method beautiful specimens may sometimes be obtained inside of half an hour, while in other instances it may be necessary to stain longer.

THE PARASITE OF TERTIAN FEVER.

The earliest forms of the tertian parasite begin to appear in the blood during the latter part of the paroxysm or just after it. They are small colorless bodies (Plate I, 1, 2, 3, 4) which fill but a small part of the corpuscle. They have appeared to us to lie within the corpuscle, and not upon it, as Laveran believes. We have never seen hyaline bodies which were engaged in the process of entering the corpuscles or which appeared to be attached to them previously to the probable entry, as Mannaberg believes he has observed. When in the resting stage they are round and apparently disc-shaped, this form being very possibly due to the shape of the corpuscle in which they lie.

When one examines the fresh blood, they appear as pale bodies which, while they seem to have no color of their own, do not show the complete lack of color and the sharp outline which is characteristic of certain vacuoles commonly observed in some of the red corpuscles in fresh preparations, particularly in the blood of anaemic patients. On examining carefully one of these bodies, one gains the impression that he is looking through a thin layer of haemoglobin containing substance with which the body is covered; that is, it would appear to lie in rather than upon the corpuscle. In this stage the organism is usually actively amoeboid. It suddenly changes its shape, often assuming rapidly the shape of a cross or of a star with four or more arms, becoming then often even more irregular, and finally, perhaps, returning again to its original disc-like shape. In the fresh specimen there is, at this stage, no indication whatever of a nucleus, unless, perhaps, the centre of the body, where the nucleus probably lies, has a more transparent and paler appearance than the outer part, which seems a trifle thicker and more refractive. Sometimes the small body may assume the shape of a ring, owing generally to the meeting and fusing of the pseudopodia (Plate I, 5). In the middle of this ring lies apparently a bit of the corpuscular substance. As time passes on, this small body increases in size and begins to develop reddish brown pigment granules (Plate I, 5, 6, 7). These granules are at first very minute. They are irregular in size and shape, appearing sometimes as small, irregular fragments, sometimes as minute rods. They are generally in very active motion, a motion much more marked than the ordinary Brownian movements. This activity would appear to be communicated by lively undulations of the protoplasm in which the pigment granules are contained. At this stage in the development of the organism, one commonly sees, on looking at a specimen of fresh blood, what, at the first glance, would appear to be collections of minute granules scattered throughout different parts of certain corpuscles, and the first impression is usually that the corpuscle contains several distinct haematozoa. Almost invariably, however, upon careful search, it may be noted that these little groups of pigment granules are contained in the bulbous extremities of the pseudopodia of a single extremely amoeboid organism. The pigment tends to collect at the extremities of the pseudopodia, while the index of refraction of the protoplasm of the organism differs so little from that of the surrounding corpuscle, that it is sometimes almost impossible to distinguish the outlines of the body. With the growth of the organism and the development of pigment, the red corpuscle which harbors the body becomes paler and usually expands, showing a diameter appreciably larger than that of its unaffected neighbors. As the organism increases in size, and pigment accumulates, its amoeboid properties become less marked while the pigment, which may still be extremely active, tends to seek a peripheral arrangement (Plate I, 7, 8). Before the end of forty-eight hours the organism has usually completely filled the red corpuscle, the pigment granules are greatly increased in number, and about the full grown body which is now about the size of the normal red corpuscle, may be traced only the pale shell-like outline of the expanded red disc (Plate I, 9). Sometimes all indications of the red corpuscle disappear. When this stage is reached, indications of segmentation begin to be seen (Plate I, 10–14). The pigment, which has formerly been so very active, becomes almost motionless, and tends to collect in the centre of the body, in the form either of a single block of pigment or a close collection of granules. The substance of the organism about this central clump assumes a finely granular, more refractive, appearance. Shortly after this, one may notice distinct indications of a radial shading or striation which begins to appear in the peripheral part of the protoplasm and becomes steadily more marked until, finally, the central pigment clump is surrounded by from twelve to twenty or even more separate segments arranged in a characteristically rosette-like form. Each of these segments shows, usually, a central spot, which is more refractive, having been sometimes mistaken for pigment. It often looks like a central depression, and probably represents the nucleus. A little later than this we may see the central pigment clump surrounded by a mass of entirely separate round, hyaline bodies (Plate I, 14), which are in every way similar to those already described as the first stages in the development of the organism. At this time, also, one begins to notice the appearance of similar small hyaline bodies in some of the red corpuscles. We have thus a very suggestive chain of evidence in favor of the view that this is a reproductive process; that these hyaline segments resulting from the division of the organism are identical with the fresh hyaline forms that appear in the red cells. Commonly, however, segmentation does not occur with quite such regular figures. The smelting, so to speak, of the granules into a solid block may not occur, and the segmentation may take place before the granules have all collected in the centre. Again, instead of the regular radial arrangement of the segments, we see the organism break up throughout its substance into a number of round, hyaline bodies, with central refractive points (Plate I, 13), while later on we find the central pigment mass surrounded by a group of separate hyaline bodies. We have never seen figures corresponding exactly to Golgi's first form of segmentation, where he shows the pigment left in a central protoplasmic body, while a peripheral layer of protoplasm alone segments. We have not been able to make out a distinct double outline in the case of the spores, as Antolisei asserts that he has done. Not infrequently, at the time when we observe full-grown organisms in the blood, as well as during the days when only half-grown forms are to be seen, occasional pigmented bodies may be found outside the red corpuscles free in the plasma. Some of these represent entirely full-grown bodies which have destroyed the surrounding corpuscle (Plate I, 18), while in other instances the half-grown forms may actually leave their host (Plate I, 21). This process may be occasionally observed under the microscope. The corpuscle containing the parasite suddenly collapses like a bladder, its color becoming immediately diffused into the surrounding plasma, while the parasite at the same moment bursts out of the corpuscle into the serum. Almost immediately after its escape from its host, the free parasite becomes irregular in outline, or fragmented. The pale decolorized expanded shell of the corpuscle may sometimes be distinguished for a short time after the escape of the parasite. This bursting of the half-grown form from the corpuscle has been well described, also, by Bastianelli and Bignami. The budding or breaking up of the extra-cellular forms into several small bodies, is very commonly observed (Plate I, 19–20). The large extra-cellular forms are often several times the size of the normal red corpuscle. They have generally a pale, transparent, swollen look. The outlines are indistinct, while the pigment is commonly extremely active. After observing these bodies for a time, certain changes are often seen to take place.

(1). The pigment remains for a considerable time extremely active, while the outlines of the body become very indistinct and somewhat irregular, and the whole parasite becomes more and more expanded until it reaches almost the size of the ordinary polymorphonuclear leucocyte. Gradually the motion of the pigment becomes less active, the outlines more irregular, till finally there remains only a misshapen mass of protoplasm containing fine brown motionless granules, a picture very similar to that drawn by Laveran in his description of the swollen, cadaveric forms.

(2). The large extra-cellular forms very often become fragmented. A small prominence will be noted upon one side of the body, which rapidly becomes shut off from its mother form, forming a separate circular pigmented body. In this manner, one large form may give rise to four or five smaller bodies. The motion of the pigment may be quite active, but very commonly after a short time it becomes less marked, the outline of the bodies becoming indistinct, until they remain as pale shadows in the field. Not infrequently one sees several of these small bodies, the results of fragmentation, connected together by thread-like processes in which pigment granules may be seen (Plate I, 21). This process of budding and fragmentation we believe to be degenerative in nature.

(3). Not uncommonly, one of these large, swollen, extra-cellular bodies may be seen to develop a pale vacuole-like area usually of a disc-shape, in which sometimes one or two bodies resembling segments may be seen. About this area, a number of small irregular vacuoles develop, while the pigment between them is often very active. As time goes on, and the vacuoles increase in number, the pigment generally becomes motionless, lying as small brown or black specks between the vacuoles (Plate I, 23, 24). Often one of these bodies, filled with vacuoles, may assume a most irregular shape. These elements we believe, with Antolisei, to be degenerative, and not, as Golgi suggested, regenerative forms; for, notwithstanding the fact that the round bodies seen in the large clear area are not dissimilar to the segments seen in the other forms of segmentation, as one observes them in the fresh specimen, the vacuolization of the rest of the substance, the irregularity of the shape, and, more important than all, the fact that these bodies do not stain in a characteristic manner, leads us to believe that they are degenerative.

(4). Another change often noted in these large, extra-cellular organisms, is the development of the so-called flagellate forms. Here the pigment assumes at first a particularly active motion. It dances with surprising rapidity, while now and then at the periphery of the organism we may note marked wave-like protrusions and undulations. Suddenly the granules assume a more central position, still being extremely active, while at the same moment one or more thread-like processes, several times the length of the organism, break out from different parts of the periphery (Plate I, 22). These flagella show often a slight swelling at their extremity, and occasionally other olive-shaped swellings at one or more points in their course. Sometimes granules of pigment may be seen in the flagella. Often the body from which the filaments come gives off buds, or fragments into several smaller pigmented bodies, all of which are moved about with great activity by the mobile flagella. The length of time during which these motions may exist varies; sometimes they may be observed for as long as half an hour. Sometimes the flagella may break off from the main body; but with the breaking off of the flagellum, its power of individual motion does not cease, and free flagella are not infrequently seen, making their way about among the red corpuscles. They have in this stage quite the appearance of spirilla, such as occur in relapsing fever.

Phagocytosis, as pointed out by Golgi, occurs, generally speaking, at stated intervals in tertian fever; that is, at the time of the paroxysms. Wherever segmenting bodies are seen, we may observe pigmented leucocytes, and the pigment in these leucocytes is generally in the form of large blocks, similar to those left after the segmentation of the parasite. But this free pigment is not the only constituent of the malarial parasite which is taken up. Commonly, the small, extra-cellular bodies, which result from the breaking up of the large, full-grown, swollen, extra-cellular organisms, are also taken up, a process which may be observed under the microscope. Again, the same fate may befall the half-grown bodies which break out from the corpuscles, so that at times pigmented leucocytes may be seen at a considerable distance from the paroxysm. The very best opportunity which we possess for studying phagocytosis under the microscope is offered us, however, in the presence of the flagellate bodies. Wherever flagellate bodies develop, we may almost invariably observe the active process of phagocytosis. The appearance of flagella seems to be, in most instances, the signal for an attack upon the parasite by the surrounding leucocytes. Not all the varieties of leucocytes appear to take part in this warfare. While pigment granules are very commonly found in mononuclear elements in the circulating blood, we have never seen a mononuclear leucocyte attack a flagellate body under the microscope. The "multinuclear" neutrophiles appear to monopolize this function in the fresh specimen, and at times we have seen a single flagellate body attacked by as many as three leucocytes at once. We have never seen a lymphocyte or small mononuclear form containing pigment, nor have we ever seen any indication of phagocytosis among the eosinophilic leucocytes.

We believe, then, that we can trace in the blood the life-history of the tertian organism, beginning with the hyaline body directly after segmentation, and ending, after nearly forty-eight hours, with the full-grown form which has destroyed the red corpuscle, while the process of reproduction is represented by the segmenting forms of Golgi. The segmenting bodies, as has been noted by Antolisei (129) and Bastianelli and Bignami,(152) are disproportionately scanty in comparison to the number of adult forms seen some hours before the paroxysm, a fact which is doubtless explained, as pointed out by these observers, by their greater frequency in the spleen. The segmenting bodies are usually at first surrounded by the pale rim of a decolorized red corpuscle. This is often so pale that it is overlooked; it shows more distinctly in colored specimens. In the more advanced forms this rim may be no longer distinguishable. The segmenting bodies which are observed in the peripheral circulation are usually about the size of a red blood corpuscle, sometimes larger, sometimes smaller. Occasionally we have found smaller segmenting bodies contained in red blood corpuscles which show relatively little decolorization (Plate I, 16, 17). We have not been able to definitely associate these forms with anticipating fevers, as Bastianelli and Bignami (153) have done to their satisfaction. The large extra-cellular forms, with pale protoplasm and dancing granules, are probably, in some instances, degenerative forms, but we do not feel that there is as yet sufficient proof to warrant the assumption that this is true in all instances. We have seen segmenting bodies develop from some quite large forms. There are, also, some reasons which would suggest that the flagellate forms are, as so many persons believe, degenerative in nature, but we do not feel at present quite ready to accept that view.

We find that the fever keeps pace with the development of the organism, the paroxysm being invariably associated with the segmentation of the full-grown bodies and the appearance of the fresh group of young individuals. The presence of segmenting forms is always, in our experience, an indication that the paroxysm is impending or has already begun. Not infrequently these forms may be seen several hours before the onset of the paroxysm, but never have we seen segmenting bodies in tertian fever without their being definitely connected with a paroxysm.

Double Tertian Infection. Multiple Infections.

Such, then, is the course of development of the tertian parasite as we observe it in studies of the fresh blood. More commonly, however, we have a somewhat more complicated picture: namely, the presence of two instead of one group of parasites. Thus, for example, if we examine the blood during the paroxysm, we find not only full-grown segmenting forms, and perhaps fresh hyaline bodies, but also another set of organisms which show the development characteristic of about twenty-four hours' growth; in other words, there is a double infection, two sets of organisms, becoming mature on successive days, and, as one might be justified in expecting, the clinical picture in these cases is one of quotidian fever. It is probable that in some instances there may be still further complications by infection with more than two groups, or by infections with organisms which are not so sharply distinguished into separate generations as in the great majority of instances.

THE PARASITE OF QUARTAN FEVER.

This parasite, in its earliest stages of development, is scarcely distinguishable from the organism of tertian fever. The youngest forms are small hyaline, amoeboid bodies, filling but a small part of the red corpuscle. The very earliest forms are quite indistinguishable from the tertian parasite, but as they begin to grow, certain differences are readily made out. In the first place, they show a much sharper outline than the tertian parasite, while the protoplasm has a somewhat more refractive character, and the amoeboid movements are slower and much less extensive (Plate I, 26). The first forms, as in tertian fever, appear with the paroxysm, and shortly afterwards begin to develop pigment granules (Plate I, 27). These granules, however, differ a little in appearance from those in the tertian parasite. They are generally a little larger and also a little darker in color. While the pale, yellowish-brown granules of the tertian parasite are always in very active motion, these larger darker granules lie almost motionless, arranged generally about the periphery of the somewhat refractive, colorless parasite. In these young pigmented forms, there is still a certain amoeboid movement, but it is slow and lazy as compared to the rapid changes of outline which are seen in the tertian parasite. As the parasite grows and the pigment increases in quantity, the red corpuscle does not become decolorized and expanded, as does the corpuscle containing the tertian parasite. On the other hand, the infected corpuscles are usually a trifle smaller than their unaffected neighbors, while the color is, if anything, a little darker than the normal. They are also more refractive and sometimes there is a distinctly greenish, brassy appearance (Plate I, 28–34). At the end of from 64–72 hours, the parasites have reached their full development. They are then round or ovoid bodies, somewhat smaller than the normal red corpuscle; about them may be seen a very thin layer of still colored, refractive, haemoglobin-containing substance. In this stage, the amoeboid movements of the bodies are entirely lost, while the pigment, which tends to be peripherally arranged, is coarser and darker than in the tertian parasite, the individual granules differing also more markedly in size; these pigment granules are almost motionless. The index of refraction of the protoplasm is quite high, and the picture is quite different from that presented by the tertian parasite, so much so that the organisms may be readily distinguished by the skilled observer on the first examination. At this time some of these bodies may seem to have entirely destroyed the corpuscle, remaining apparently free in the serum (Plate I, 35). On staining, however, most bodies show evidence of a slight layer of corpuscular substance about them, and it is a question of doubt in our minds as to whether any true segmenting bodies are not, in the beginning, contained in the shell of the red corpuscle. Six to eight to ten hours before the febrile paroxysm begins, some of these full-grown bodies begin to show certain striking changes (Plate I, 36–39); the pigment granules which, though scattered throughout the body, have tended toward a peripheral arrangement, begin to collect at the centre. The process of the accumulation of the pigment in the centre of the quartan organism gives pictures which one does not see in the case of the tertian parasite, namely: the arrangement of the pigment in a star-shaped form, as though it tended to arrive at the centre of the body through certain definite currents which flow inward from the periphery. Finally, the pigment is collected in a central clump or solid block, while the protoplasm of the organism becomes somewhat more refractive and of a slightly granular appearance. A radial shading begins to be evident, similar to that observed in the tertian parasite, and finally the protoplasm divides into from six to eight to ten to twelve small pear-shaped leaflets, each containing a central more refractive point. The regularity of the arrangement of these leaflets is decidedly more marked than in the case of the tertian parasite, most exquisitely symmetrical marguerite forms being at times observed. Later on, these pear-shaped leaflets separate from the central mass and are seen as small, round or ovoid bodies surrounding the central pigment clump. Simultaneously with this we may note the appearance of fresh hyaline forms in certain of the red blood corpuscles. Some of the full-grown parasites do not segment on reaching their complete development, but undergo certain changes similar to those observed in full-grown tertian organisms:

(1). The pigment granules, which have previously been extremely lazy in their movements, may take on a considerable activity, while the body may expand, equalling or even slightly exceeding the size of a normal red corpuscle (Plate I, 40). These bodies are very transparent, and closely resemble the analogous forms of the tertian parasite. Eventually, the movements of the pigment become less marked, the outlines of the body become irregular and indistinct, and a motionless cadaveric form remains.

(2). Forms similar to those just described may undergo a further change, namely: fragmentation into a number of small bodies, which eventually become indistinct and deformed, just as in the case of the tertian parasite.

(3). Vacuolization of these forms we have also observed (Plate I, 42).

(4). These bodies may develop flagella just as in the case of the tertian parasite (Plate I, 41). The granules become suddenly very active, collecting at a given moment more toward the centre of the body, while long, thin, flagella burst from the contour, making active, serpentine movements among the surrounding corpuscles. These forms differ from those of the tertian parasite in their smaller size and in the greater coarseness of their granules. The movements of the flagella are not, so far as we can make out, essentially slower than those in the tertian organism. As the parasites are smaller, and the granules darker and larger, the complete bodies resemble much more closely the forms about to be described in the aestivo-autumnal parasite, than those developing from the tertian organism. Flagellate bodies were observed in two of our five instances of quartan fever.

Phagocytosis is observed in quartan infection with the same extreme regularity as in tertian fever. It begins with the paroxysm and lasts during it and for several hours afterwards. The forms taken up, as in the case of tertian fever, are the central pigment clumps, the small, fragmented, extra-cellular forms, the flagellate bodies, and not infrequently the segmenting bodies. In a number of instances we have been able to follow, under the microscope, the engulfing of an entire segmenting body by a "multinuclear" leucocyte. In other words, the extra-cellular forms alone are usually taken up by the phagocyte.

Double and Triple Quartan Infections.

As, in tertian infection, two or more groups of parasites, showing different stages of development, may be present in the blood, so in quartan infection, this is a very common occurrence. Sometimes we may see two groups of quartan organisms which reach maturity on successive days. As the febrile paroxysm is always associated with the segmentation of a group of parasites, we see, in these instances, paroxysms on two successive days, with one day of intermission,—*double quartan fever*. Again, with considerable frequency, we may see three groups of organisms, which, reaching maturity on successive days, cause daily paroxysms—*triple quartan infection*. Three of our five cases of quartan fever were triple infections. It is probable, as has been noted in the summary of the literature, that infection with multiple groups of parasites may take place, causing irregular febrile manifestations, though this we have not, in our limited number of cases, been able to observe. We have, then, distinguished a parasite which differs from the tertian organism in several distinct manners:

(1). *The length of the cycle of development,* which lasts forty-eight hours in the one case, and seventy-two in the other.

(2). *The appearance of the organism itself;* pale and indistinct in the tertian; sharply outlined and somewhat refractive in the quartan; actively amoeboid in the former; slightly amoeboid in the earlier, and motionless in the later stages in the latter.

(3). *Character of the pigment;* often a reddish-brown in the one; coarser, more irregular in size, and darker in the other; actively motile in the former; lazy and almost motionless in the latter.

(4). *The volume;* reaching the full size of the red blood corpuscle in the tertian; never reaching so large a size in the quartan; the large, full-grown, free (degenerative?) forms being sometimes twice as large as the red blood corpuscle in the former; rarely larger than the red corpuscle in the latter.

(5). *The segmenting forms;* usually as large as the red corpuscle in the one; not as large in the other; the segments numbering usually from fifteen to twenty in the former; from six to twelve in the latter; the whole organism breaking not infrequently into irregularly arranged segments in the former; typical rosette forms almost always in the latter.

(6). *Behavior of the infected corpuscle:* The corpuscle becomes expanded and decolorized in the tertian infection; shrunken and often brassy-colored in the quartan.

It is not just, as some of the critics have done, to assert that the chief difference between the quartan and tertian parasites consists in the number of their segments. There are differences which the skilled observer can detect in every stage of development, unless it be in the very earliest forms,—those immediately following segmentation.

In tertian infection, while many full-grown and nearly full-grown forms are to be found some hours before segmentation, at the time of segmentation the bodies observed in the peripheral circulation are distinctly less frequent; the explanation is, probably, that segmentation takes place for the most part in the internal organs. This is, however, not true of the quartan parasite. Here all stages are seen with equal frequency in the peripheral circulation, and segmenting bodies may be found where very few organisms are present. In tertian fever, for instance, it is extremely rare to see segmenting bodies in cases where they are not associated with a definite febrile paroxysm. In quartan fever, on the other hand, one may follow the entire life-history of a single group of parasites for weeks, where the number of organisms is so slight as to produce little or no visible febrile reaction.

THE PARASITE OF ÆSTIVO-AUTUMNAL FEVER.

The third type of organism which we have been able to distinguish, is identical with that which has been described by Sacharow as the organism of Febris irregularis, the Haematozoon falciforme of Antolisei and Angelini, the aestivo-autumnal parasite of Marchiafava and Celli. This type of organism shows quite marked differences from the forms above described. The youngest forms of the parasite are quite similar to those observed in tertian and quartan fevers; they are small hyaline bodies. There are, however, certain differences which may be striking. The hyaline forms are usually smaller than those of the tertian parasite, while they are generally more highly refractive. They often have a decidedly ring-like appearance (Plate II, 1, 2), which is probably in most instances only apparent. These ring-shaped bodies are very small—the smallest seen. The outer layer of the parasite shows quite a sharp glistening refraction, while the central part is shaded, appearing as though it were thinned, the coloring of the corpuscle showing through. While observing one of these very small, refractive, ring-like forms, we not uncommonly see it become suddenly expanded, more homogeneous, and paler (Plate II, 3–6). The outer rim no longer seems more refractive and thicker than the centre, and the ring-shaped appearance is lost. A wavy undulation of the border is commonly to be seen, while, very frequently, most active amoeboid movements develop, similar in every way to those of the tertian parasite. Sometimes, in this stage, we may see two pseudo-podia join one another, enclosing a central piece of corpuscle, thus causing a true ring. While in the organisms of tertian and quartan fever we have been able to follow out and to trace the length of the cycle of development with perfect clearness, we have not been able to do this with the same accuracy in the case of the aestivo-autumnal organisms. This difficulty is due, in part, to the fact that the earlier stages of development only are found in the peripheral circulation, the later stages in the cycle occurring in the spleen, marrow, and other internal organs, and, in part, to the fact that in most cases, when they come under observation, several groups of organisms are present at the same time. We are inclined to believe from our observations that the length of the cycle is subject to great variations, amounting, in some instances, to twenty-four hours or less, and in others to forty-eight hours, or even more. The small hyaline forms above described, appear, usually, during and shortly after the paroxysm. In a variable length of time after this, pigment granules begin to make their appearance. These are not, however, numerous and active as in tertian infection, or coarse as in the quartan. Often, only one or two most minute dark granules appear in the periphery of the homogeneous, disc-shaped organism (Plate II, 7–12); sometimes, in the more ring-shaped refractive variety, they may be situated at the inner edge of the more refractive border, close to the central pale area, though more commonly they are observed, as in the more expanded forms, just at the periphery. The pigment granules show but little movement. Before the appearance of the pigment, the organism increases somewhat in size; rarely, however, does its diameter exceed a third that of the red corpuscle itself. The corpuscles in which these bodies lie, show no indication of decolorization. Not infrequently, however, they are shrunken, often crenated or spiculated, and of a deeper brassy color ("globuli rossi ottonati"), an alteration indicating, probably, degenerative changes in the corpuscle (Plate II, 7, 16). In some cases we may see corpuscles containing small, refractive, ring-like bodies, with or without pigment, where the haemoglobin seems to have left the outer part of the disc and collected about the parasite, leaving the outer part decolorized though still showing the outline of the original corpuscle (Plate II, 13). The haemoglobin here shows generally the brassy green color. Later on we may see in the larger forms of the organism a small collection of non-motile or slightly motile pigment granules about the centre of the body (Plate II, 13, 16–19). This is seen only in the larger forms, forms which may have a diameter more than one-third the size of that of the red corpuscle. The pigment, however, in these instances is never as profuse as in the tertian form. With these bodies, which occur only before and during the paroxysms, certain still more characteristic forms may be seen in the circulating blood, forms which we have never seen excepting in association with the paroxysm. Here, in similar bodies, those which are, perhaps, a trifle more than one-third the size of the cell in which they are contained, a few pigment granules may be seen to have gathered together near the centre, and to have become smelted, as it were, into a solid clump, while the surrounding body has a peculiarly homogeneous, refractive appearance (Plate II, 14, 15, 20). These forms, as we have said, have only been noted just before or during the paroxysms. They are always associated with pigment-containing leucocytes, while the pigment in these leucocytes is usually in the form of similar blocks. Occasionally these bodies may reach nearly the size of a normal red corpuscle. From the fact that these forms are observed only during the paroxysms, from the fact that we have never seen these solid blocks of pigment in tertian or quartan fever, excepting in segmenting forms, from the fact that they are always associated with leucocytes containing similar blocks of pigment, we might easily conclude, even had it not been proven by the examination of the splenic blood, that these are early or pre-segmenting forms. We have never seen actual segmenting forms in the circulating blood, as described by Sacharow,(212) possibly because we have not had so large a number of severe cases to deal with. During the early part of the paroxysm, indeed, and for several hours before, very few organisms are to be found in the peripheral circulation. In several instances at this stage we have been unable to find any, while some hours later the organisms were present in large numbers. We have not carried out a systematic study of the splenic blood, though in several instances we have found, on puncture, segmenting forms similar to those described by Marchiafava, Celli, and Bignami. Examination of the splenic blood at the beginning of the paroxysm reveals always a large number of intracorpuscular parasites with central pigment blocks, as well as a certain number of similar organisms, which are free.

The advanced segmenting forms, which we have seen, have showed no traces of the surrounding blood corpuscle (Plate II, 21–24). Both in the number of segments and in the manner of division, the segmenting aestivo-autumnal parasite resembles closely the similar stage of the tertian organism. It is, however, much smaller, as is shown in the plate.

As has been said above, we have not been able to sharply define the length of time required for this cycle of development. We believe, however, that it varies considerably from twenty-four hours, or even less, to forty-eight hours, or somewhat more. In a majority of instances, where the fever has lasted more than one week, other characteristic bodies may be noted in the blood. Here, at first, one may notice more of the larger rounded bodies with central pigment granules. Commonly, these assume an elongated or ovoid shape. Occasionally, forms may be seen nearly as large, or larger, than the corpuscle. These show a peculiarly refractive appearance, the pigment granules become more numerous, coarser, and show a tendency to a ring-like arrangement in the centre. The bodies lie usually at one side of the red corpuscle, the remains of the cell forming a bib-like attachment, as it were, upon the other side (Plate II, 26–33). Often the red cell becomes much decolorized; sometimes it shows a crenated outline. Finally, we see still larger forms, which are usually ovoid or crescentic in form, the remains of the red corpuscle forming a convex bib, connecting the two horns of the crescent, or attached to one side of the ovoid form. Sometimes the crescentic or ovoid bodies may lie in the middle of the cell (Plate II, 25); more often, the remains of the cell are attached to them as a bib. Some of the apparent separate ovoid bodies are, probably, simply crescentic forms which are viewed through the microscope from the convex side of the crescent. This may at times be clearly shown by the revolving of one of these bodies on the slide. These forms are highly refractive, so much so that the outer border has been described as a double outline, and interpreted as a capsule. Whether this apparent double outline represents an actual capsule, or only a thickening of the outer parts of the body, we do not feel quite certain. We have never been able to observe that this so-called double outline showed a coloring with haemoglobin, as described by Antolisei and Angelini.(119) The pigment granules are coarse, often in the form of rods collected about the centre in a clump, or not infrequently in a ring. Finally, we see large crescentic or ovoid bodies, averaging eight to nine micromillimetres in length; the red corpuscle in which they have developed is represented by but a small, faintly-colored attachment upon one side of the ovoid, or at the concavity of the crescent, while, in some instances, all trace of the corpuscle may be absent. At times one may observe actual changes from the ovoid bodies into the crescentic forms, or the converse, beside the occasional picture of the revolving crescent before referred to. Often, in association with these crescentic and ovoid bodies, we may also see a number of somewhat smaller round bodies (Plate II, 34, 35, 38); indeed, at times, we may trace the change from a crescent or an ovoid form into one of these round elements. The round bodies do not as often show a "double outline," nor are they, as a rule, quite as refractive. In the crescents and the ovoid and round bodies, we see, occasionally, changes which show a certain analogy, as Antolisei and Angelini (119) have pointed out, to processes occurring in the large full-grown tertian forms:

(1). Sometimes, for example, one of these bodies may show one or more small protrusions from the surface, which may, indeed, be cut off from the rest of the body as small, clear, hyaline droplets (Plate II, 30, 36). This is the gemmation which, by some of the earlier observers, was supposed to be a reproductive process.

(2). Again, we may see the development of a large number of small vacuoles of different sizes; the parasites at the same time lose their sharp refraction, becoming pale and more indistinct (Plate II, 37); this process is clearly degenerative in nature.

(3). Lastly, whenever these round bodies occur, flagellate forms may be seen to develop (Plate II, 38–40). These flagellate bodies are distinctly smaller than those of the tertian parasite, being much more similar to the quartan forms. The pigment collects frequently in the shape of a ring in the centre of the organism, and assumes the same active movements that one sees in tertian fever, while the periphery of the body shows the same violent undulations which suggest so strongly that some body within the parasite is trying to escape; and just as in the tertian parasite, one or more active flagella eventually break forth. The same breaking off of the flagella, the same budding and fragmentation of the body, the same phenomena of phagocytosis, are noted here as in tertian infection.

The small hyaline and slightly pigmented forms disappear quite rapidly after the administration of quinine, though they are considerably more resistant than the similar forms of the tertian or quartan parasite. The crescentic and ovoid bodies, however, may remain for a very long period, notwithstanding large and continued doses of quinine. In cases where quinine is given during the first week of the disease, the organisms disappear in the majority of cases without the occurrence of crescentic bodies, a fact which would tend to show that the formation of the ovoid and crescentic forms does not occur before the end of the first week. In the cases where we have found crescentic and ovoid bodies alone in the blood, fever has rarely been noted, the febrile paroxysm always being associated with, or followed by the presence of small hyaline and amoeboid bodies.

In our studies, then, which have been mainly conducted with fresh blood, we find a type of organism quite separate from that of ordinary tertian or quartan fever. The cycle of existence of this parasite begins with a small hyaline body which, when it has reached its full development, is rarely half the size of the red corpuscle. During its growth, marked changes (crenation, brassy color, retraction of haemoglobin) are often caused in the red corpuscles. The advanced segmenting forms are rarely seen in the blood current, though pre-segmenting bodies (bodies with central pigment) are not infrequently observed. The process of segmentation, and probably the greater part of development, goes on in the internal organs. We have been unable to trace a constant length of the cycle of development, and we have been unable further to separate two or more types of the parasite depending either upon the length of the cycle of development or upon any other morphological or biological differences. We believe that the length of the cycle varies greatly in different cases, lasting usually from twenty-four hours or even a little less, to forty-eight hours or more. After the infection is five days or a week old, certain of the organisms, instead of segmenting, pursue a further growth, developing into the hyaline, refractive, ovoid and crescentic bodies which show a particular resistance to quinine, having been considered by many to be encysted forms. Do these crescentic bodies represent forms with a longer cycle, giving rise to fevers with long intervals between the paroxysms, as Canalis,(104) Golgi,(118) Antolisei,(131) and others believe? We do not feel justified in making positive statements concerning this point. We have never observed segmentation of the crescentic, ovoid or round bodies, though the frequency of relapses in cases where they are found suggests the possibility of its occurrence. We have, on the other hand, seen processes of vacuolization and of gemmation, which we believe to be degenerative in nature.

We have met with nothing in our observations suggesting that the crescents are conjugate forms, as is believed by Mannaberg.(291)

Phagocytosis we have observed here, as in tertian and quartan fevers, particularly at the time of the paroxysm, though pigmented leucocytes are found occasionally at all stages of the cycle. The presence of the large mononuclear macrophages, described so well by Bastianelli,(346) we have found very rarely in the peripheral circulation. While mononuclear elements with pigment are not uncommon, we have never seen the act of phagocytosis performed under the microscope by a mononuclear leucocyte, while we have many times seen the engulfing of flagellate bodies by the polymorphonuclear neutrophiles.

V.—GENERAL ANALYSIS OF 544 CASES IN WHICH THE TYPE OF ORGANISM WAS CLEARLY DISTINGUISHED.

Of these 616 cases, in 542, not including the two relapses, the type of parasite was definitely differentiated. The following table shows the number of cases of each type observed in the hospital and out-patient department:

		Hosp.	Disp.	Total.
Infection with the tertian parasite.	Single tertian infection......	57	93	150
	Double " "	116	72	188
Infection with the quartan parasite.	Single quartan infection......	2	0	2
	Double " "	0	0	0
	Triple " "	3	0	3
Infection with the aestivo-autumnal parasite..........................		104	84	188
Combined infection with aestivo-autumnal and tertian parasites....		9	2	11
		291	251	542

It is interesting to note the greater frequency with which single tertian infection was seen in the dispensary than in the hospital—93 cases occurring in the dispensary from a total of 251, and 57 in the hospital out of a total of 291. This is doubtless due largely to the fact that the cases of mild malarial infection are unwilling to enter the hospital, while the double tertian cases and the aestivo-autumnal infections, which are more severe, are more ready to enter the wards.

The tables below show the relation of the different types of malaria to the time of year:

		Jan.	Feb.	Mar.	Apr.	May.	June	July.	Aug.	Sept.	Oct.	Nov.	Dec.	Tot'l.
Tertian.	Single....	5	1	7	16	20	14	27	14	17	19	7	3	150
	Double...	2	5	8	9	12	13	23	27	30	43	10	6	188
	Total.....	7	6	15	25	32	27	50	41	47	62	17	9	338
Quartan.	Single....	0	0	0	0	0	0	0	0	0	0	1	1	2
	Double...	0	0	0	0	0	0	0	0	0	0	0	0	0
	Triple....	0	0	0	1	0	0	2	0	0	0	0	0	3
	Total.....	0	0	0	1	0	0	2	0	0	0	1	1	5
Aestivo-autum...		1	0	1	0	1	2	17	18	65	55	18	10	188
Combined Aestivo-aut. and Tertian.		0	1	1	0	0	1	2	0	0	5	0	1	11
Total..........		8	7	17	26	33	30	71	59	112	122	36	21	542

Thus in the first half-year there were:

Tertian infection.	Single..	63
	Double..	49
		112
Quartan infection.	Single....	1
	Double..	0
	Triple..	0
		1
Aestivo-autumnal infection..............................		5
Combined infections......................................		3
Total..		121

While in the second half-year there were:

Tertian infection.	Single..	87
	Double..	139
		226

Quartan infection.	Single	1
	Double	0
	Triple	3
		4
Aestivo-autumnal infection		183
Combined infections		8
Total		421

These tables show in an interesting manner how the severity of the type of infection increases as the summer and fall approaches; thus, in the first half-year we have more single than double tertian infections, while in the second half-year, when malarial fever assumes a more severe type, we have nearly twice as many cases of double tertian as of single tertian infection. The increase in severity of the malarial fevers becomes more evident when we observe the course of the aestivo-autumnal cases. While in the first half-year only 5 cases were noted, a little less than one twenty-fourth of the total number of cases observed, in the second half-year we see 183 cases, or nearly an half of all the cases which occurred.

Thus, it may be seen that with the earliest cases of malarial fever in the year, the mildest types of infection are met with,* the single tertian type predominating. As the season advances, and the months approach which are richest in malaria, the single tertian cases become less frequent and the double tertian infections more common, while at the height of the malarial season a majority of the cases are of the aestivo-autumnal, the most severe type in this climate. Marchiafava and Celli(144) have, in some of their writings, been inclined to believe that a patient suffering from one malarial infection may show the organisms and the fever characteristic of aestivo-autumnal malaria during the fall, and later, in the spring, without a new infection, simply as a relapse, show the regular types of fever, tertian or quartan, with their characteristic organisms. In a number of our cases, patients who had suffered, for instance, with aestivo-autumnal malaria during the fall, have, in the following spring, had a characteristic tertian or double tertian infection, or the converse. In none of our cases, however, has it appeared to us that these were true relapses, all of them giving histories, and having been subjected to circumstances which would wholly justify the assumption that a second infection had occurred. Against this view, also, speaks the course of the infection in cases of aestivo-autumnal fever, which, having arisen in tropical climates, come to Baltimore in the spring months. This was the case in two of the five instances of aestivo-autumnal fever admitted in the first half-year. One of these cases originated in Jamaica, the other in Cuba. In neither instance did the organisms or the progress of the case differ in any way from the ordinary aestivo-autumnal infections, though they occurred at a time of year when the milder tertian infections formed the vast majority of all cases observed. Particularly striking is the history of one of the three cases of combined aestivo-autumnal and tertian infections. This man arrived in February with a fever which he had contracted in Cuba. His symptoms at the time of his arrival appeared due rather to the tertian organisms, which were preponderant, than to the aestivo-autumnal. Under quinine the fever disappeared, and the organisms were no more seen in the peripheral circulation. Seven or eight weeks later, in April, he had a relapse while still in the hospital where he had undergone an operation for the radical cure of hernia; but in this relapse only aestivo-autumnal forms—small hyaline amoeboid bodies, ovoid and crescentic forms—were seen. The less resistant tertian parasites had yielded to quinine, while the aestivo-autumnal forms persisted. Surely no better opportunity could have been offered for the change in the type of the parasite were this really possible.

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* This is an old observation, dating back to Hippocrates and Sydenham. In fact, not only were the spring tertians known to be mild, but they were even thought to be beneficial. Thus a contemporary of Sydenham, Richard Morton, whose chapters on malaria (Pyretologie Opera Medica, 1696) are unequalled at that date, says (p. 51): "Quod *Febris Intermittens verna sit Remedium Regium*; h. e., saluteferum & certerorum morborum prophylacticum, &c."

While, in our experience, we have seen nothing which would justify us in positively denying the possibility of the change of an organism from one type into another according to the influences to which it is subjected, we have seen nothing whatever to suggest that this does occur, and we are decidedly inclined to believe that the tertian, quartan, and aestivo-autumnal parasites are permanently different varieties of closely allied sporozoa.

U of M

RELATION OF THE DIFFERENT TYPES OF INFECTION TO RACE.

We have seen that the colored, as compared with the white race, presents a marked relative insusceptibility to malarial infection. Should we then expect to see, in the colored race, only the more severe types of malarial fever, or should we rather expect to find that infection once taking place in relatively unfavorable ground, the disease would pursue a milder course? Among the 27 cases of malarial infection in the colored race, where the type was clearly differentiated, there were:

Single tertian infections	9
Double tertian infections	7
Aestivo-autumnal infections	9
Combined infections	2

That is, 59.2 per cent. of the cases occurring in colored patients were tertian infections, and 33.3 per cent. aestivo-autumnal; while among the white patients, 62.5 per cent. were tertian, and 34.7 per cent. aestivo-autumnal infections. There would then appear to be no essential difference between the susceptibility of the white and the colored patient to the various types of malarial fever.

On further analysis of these cases, one point is, however, rather striking. While, among the white patients, only 43.7 per cent. of the tertian infections were single,—56.3 per cent. being double—in the colored we find 56.2 per cent. of single tertian infections, and 43.8 per cent. of double. The explanation which would naturally suggest itself is that the negro, having a certain relative immunity from malarial infection, is more resistant against the organism when the infection has once taken place; the process is thus much more likely to remain a single infection than to increase in intensity and develop, as it does so frequently in the white race, into a double infection.

VI.—ANALYSIS OF THE TYPES OF FEVER ASSOCIATED WITH THE DIFFERENT TYPES OF ORGANISMS.

In considering the 544 * cases in which the types of fever were definitely made out, we shall take up separately those cases occurring in the hospital and those cases occurring in the dispensary, noting finally what conclusions may be drawn from the combination of the cases from both sources. The studies of the ward cases were much more satisfactory. In certain ways, however, the addition of the dispensary cases makes the note more complete.

TERTIAN INFECTIONS.

There were 339 cases in which typical tertian organisms were observed. Of these, there were:

Single infections	151
Double infections	188

(1). *Single Tertian Infections.*

Of the 151 single tertian infections, 58 occurred in the hospital and 93 in the dispensary.

Cases of Single Tertian Infection Observed in the Hospital.—Of the 58 cases showing typical tertian organisms, one was a relapse of a case previously treated.

Of these 58 cases, 52 showed, either outside or within the hospital, typical tertian *paroxysms*. Of the remaining 6 cases, one gave a history of having taken a few doses of quinine whenever a paroxysm appeared, with the resulting occurrence of a chill about every ten or eleven days. Treatment was begun in this case immediately, so that it could not be studied further.

One case complained of chills at intervals of about seven or eight days.

One case gave a history of having had tertian and quotidian chills, which became irregular after the spasmodic use of quinine. There was but one paroxysm in the hospital.

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* This includes the two relapses above referred to.

One case had a single chill the day before entrance, the fever disappearing spontaneously after admission.

One case gave a vague history of occasional chills, headache and vomiting for two weeks, but showed no further fever or symptoms after the paroxysm during which he was admitted, excepting a slight rise in temperature on the fourth day.

One case, where there had been daily paroxysms before entrance, showed no symptoms after the chill during which he entered. This case was probably one of double tertian infection which was dying out; it was classified among the tertian cases because but one set of organisms was seen on entrance.

Of the 52 cases showing typical tertian paroxysms, five had had quotidian attacks sometime before entrance.

Of these 58 cases of tertian infection, 11 showed a *spontaneous disappearance* of the fever after admission. In 3 of the 47 remaining cases, the fever disappeared after one or more paroxysms without the administration of quinine.

The *average duration* of the paroxysms from the beginning to the end of the rise in temperature (above 99°) was between eleven and twelve hours (11.8).

Out of 24 cases with multiple paroxysms, ten showed, perhaps, a slight tendency toward anticipation, three toward retardation; eleven showed paroxysms occurring at the same hour.

Of these 58 cases of tertian fever, 55 cases had had, in or outside of the hospital, "*shaking*" *chills*. The other 3 had chilly sensations.

Organisms.—In all of these cases typical tertian organisms were found. In 15 of the cases segmenting bodies were noted during the paroxysm. In 5 cases flagellate bodies were noted, in three instances during the paroxysm, in the fourth a few hours before the paroxysm, and in the fifth case during apyrexia, eleven hours before the paroxysm.

Cases in the Out-patient Department.—There were 93 cases in the out-patient department in which typical tertian organisms were found. Of these, 75 gave a history of having had tertian *paroxysms*. Of the 18 who gave no history of tertian paroxysms, 3 showed their first chill on the day of consultation or upon the day before; in 3 the history was not noted; in 2 the first chill had been followed by quinine, the symptoms afterward being indefinite; in 2 there were vague general symptoms—headache, pains in the back and limbs, and other symptoms characteristic of any acute infectious process; in one case the only complaint was of haemoptysis; in the remaining 7 cases chills and chilly sensations occurred, but the patients were unable to give definite statements as to the type.

In these 93 cases, there were noted:

Chills in	79
Chilly sensations in	8
"Paroxysms" in	2
Haemoptysis in	1
Vague febrile symptoms in	1
No note in	2

In the 75 cases giving a history of having had sharply-defined tertian paroxysms, four had had, at one time or another, quotidian paroxysms.

Organisms.—In five of these cases segmenting bodies were seen during the paroxysm; in one a flagellate body was also noted.

Summary of the Cases of Tertian Fever in the Hospital and Dispensary combined.—Thus in the hospital and dispensary together there were 151 cases showing single tertian infection; one of these was a relapse. Of these 151 cases, 127 had tertian paroxysms. Of the 127 which had had tertian paroxysms, 9 had had at some time quotidian paroxysms.

In the 151 cases, there were noted:

Chills in	134
Chilly sensations in	11
"Paroxysms" in	2
Vague febrile symptoms in	1
Haemoptysis in	1
No note in	2
	151

The *average duration* of the paroxysms was between eleven and twelve hours (11.8).

Organisms.—Segmenting bodies were noted in 20 cases, always at the time of the paroxysm; flagellate bodies were noted in 6 cases,—in four instances during the paroxysm, in one shortly before it, in one eleven hours before it.

Cases.

Case 4934 is an illustration of typical tertian fever with regular paroxysms.

Man, aged 24, English, a laborer; admitted March 25th, 1892, complaining of headache and fever.

Family and personal history negative; has been living in a very malarious district. He has had chills and fever off and on for six months; gives no clear history as to type; says that he would go to bed for several days at the beginning of his attack; would then get up, and in about two weeks would have another attack. His last paroxysm occurred the day before entry. Physical examination negative, barring a large, palpable spleen, the border reaching nearly to the median line. The *blood* on the day of entry showed a large number of half-grown tertian organisms. The chart shows three typical tertian paroxysms, with a remarkable regularity as to the degree of fever, and the time of onset.

The following case (10089) is an interesting example of the so-called fever with long intervals, which, as has been shown, may depend upon the presence of any of the three main varieties of parasites.

The patient, a man aged 30, German, was admitted to the hospital on June 14th, 1894, complaining of headache and chilly sensations. Four years ago he had two chills a week apart, which were immediately stopped on the beginning of treatment. Four weeks before entry he had a shaking chill, followed by fever and sweating. A week later he had a second attack, and a week after that a third; yesterday a fourth.

Examination of the *blood* yesterday in the dispensary, while the patient was in the sweating stage, showed two or three large, extra-cellular pigmented organisms, characteristically tertian in type, with the pigment in active motion. On entrance to the hospital, the examination showed a well-nourished man, complexion sallow, herpes about nose and lips, spleen readily palpable. Sonorous and sibilant râles heard occasionally on inspiration. Examinations of the blood in the hospital were negative. The temperature remained normal until the 18th, with the exception of a rise to 99.4° on the 16th.

On the 18th, at 11.30 a. m, the patient had a chill, exactly eight days after the last. The *blood* during the chill at 11.30 a. m. showed one hyaline, intra-cellular parasite in active motion; two large, extra-cellular, full-grown bodies, with actively moving pigment.

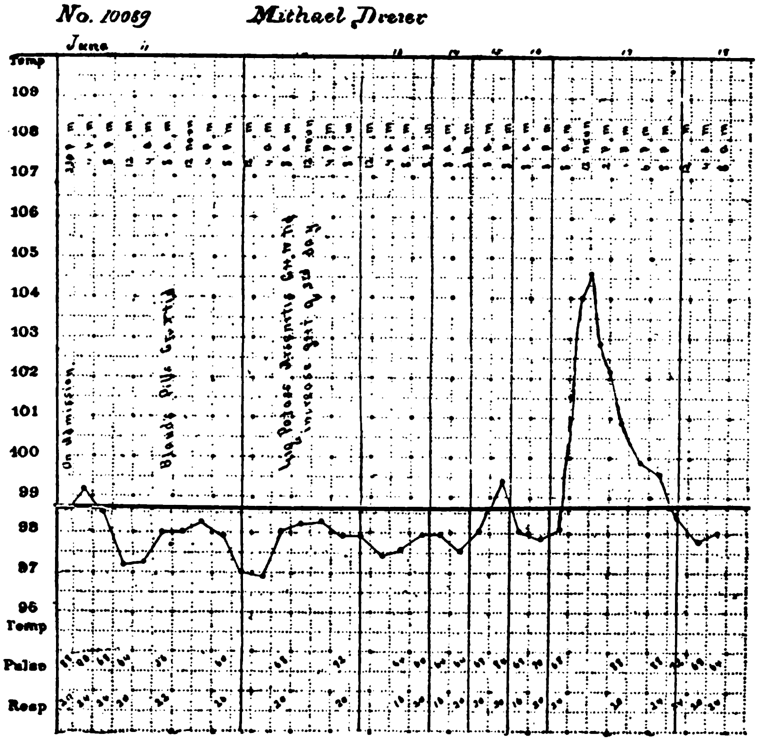
19–6–94. The *blood* showed a small number of half-grown intra-cellular pigmented parasites of the tertian type.

The patient insisted upon leaving the hospital, and was discharged with a prescription for quinine.

This is clearly an instance of tertian infection, where, with each paroxysm, the greater part of the new group of parasites was destroyed, the patient passing, as it were, through a fresh incubation period of seven or eight days between each attack.

March
Temp.
109
108
107
106
105
104
103
102
101
100
99
98
97
96
Temp
Pulse
Resp

The examination of the blood on the day of discharge makes it probable that in this attack there would have been a paroxysm on the following day, a considerable number of half-grown bodies having been found.



(2). *Double Tertian Infections.*

There were 188 cases of double tertian infection. Of these, 116 occurred in the hospital, and 72 in the out-patient department.

Cases of Double Tertian Fever occurring in the Hospital.—116 cases in the hospital showed typical double tertian infection. Of these, 114 showed characteristic quotidian *paroxysms*, either in the house or outside. The two which did not have quotidian paroxysms, had tertian fever. The first of these cases was a man 28 years of age, who gave a vague history of headache, thirst, and general debility for five days. This patient showed a slight paroxysm on the day of admission. On the following day the temperature varied between 97.1° and 100.7°. On the third day there was another slight paroxysm, the fever disappearing spontaneously after this. The blood showed on entrance two distinct sets of parasites, one group being much more numerous than the other. The case was probably one of developing double tertian infection, which recovered spontaneously in the hospital. The other case had had regular tertian chills for two weeks. On admission, the examination of the blood showed two distinct groups of organisms. There was, however, spontaneous disappearance of the fever in the house, no distinct paroxysms occurring after that during which the patient entered. This case was probably, also, one of developing double tertian-malaria, which was interrupted in its course by the favorable change of surroundings.

Of the 114 cases which had quotidian paroxysms, 20 had had tertian paroxysms at some time before entrance, while 9 gave a history of irregular paroxysms before entrance. Two cases gave no distinct history of paroxysms before entrance. One of these cases gave a history of general pains in the back and limbs, weakness, diarrhoea, and vomiting; the other gave a history of headache, abdominal pain, and diarrhoea. One of these was a foreigner, who spoke English with difficulty, and was not able to give a clear account of himself.

Four patients, who gave a history of quotidian fever outside, showed tertian fever after entrance into the hospital. One patient showed in the hospital two tertian paroxysms, the first severe, the second very mild. After this quinine was given, and recovery followed. Though the paroxysms in the hospital were tertian in character, two sets of organisms were found on entrance, and the case was, doubtless, either a double tertian infection which was dying out, or, what is not improbable, the patient's history of daily chills was incorrect, as he spoke but little English, and we were dealing rather with a beginning double tertian infection. The second case was one of a dying-out infection, only a few half-grown organisms being found on the day of entrance. No paroxysm was observed on the following day, and but a feeble one on the third.

One case had an abortive paroxysm on the day of entry and tertian attacks later, the second group of organisms disappearing.

One case was changed to a tertian infection experimentally (see page 113).

Of these 116 cases, three showed marked irregularity in the paroxysms. One case showed daily abortive paroxysms, with a tendency toward continuity. The irregular temperature followed several doses of quinine. One case was complicated with an abscess of the thigh, which probably accounted for the slight irregularity. One case was that of a child ten months of age, whose chart showed considerable irregularity in the temperature. The examination of the blood in this case showed organisms in nearly all stages of development, and it is probable that the irregularity of the temperature may be accounted for by the lack of the ordinary arrangement in groups.

Two cases showed a more or less steady elevation of temperature with daily exacerbations. The first showed rather irregular daily paroxysms, the temperature remaining elevated on one occasion for thirty-six hours. This was one of the earlier cases, and as the notes concerning the organisms are not as satisfactory as could have been wished, one cannot state whether in this case the presence of organisms in different stages of development may have had any relation to the irregularity of the symptoms.

The second case showed at first a more or less continuous temperature, with daily exacerbations; it was mistaken for a case of typhoid fever. After five days' treatment with cold baths, the temperature became quite regularly intermittent. The case is of enough interest to cite more particularly.

W. Y., aged 29, German, was admitted to the hospital on the 8th of August, 1892, complaining of loss of appetite, general malaise, and fever. His family and personal history bore no relation to his complaint at that time, which began four days before admission with loss of appetite and fever. He had had no chills, no abdominal pain, no nose bleed. He complained of shortness of breath, some cough, occasional nausea, no vomiting. There was constipation at first; later diarrhoea. The examination of the blood, which, unfortunately, was very superficial, showed no malarial organisms.

Physical examination. The patient was a large, well-nourished man; thorax and abdomen were negative on examination, except for a palpable spleen. The *urine* showed a trace of albumen; no casts seen; diazo reaction absent. Between the 8th and 10th of August the temperature ranged between 99° and 104.5°, being continually elevated. The case was believed to be one of typhoid fever, and cold baths were ordered. After the 10th of August, the patient had an irregularly intermittent temperature, ranging between 97.6° and 105.8°. He was given, in all, ten tub baths. On the 14th, by which time, as the chart will show, the temperature had become more regular in character, the examination of the *blood* showed typical full- and half-grown, intra-cellular bodies, a number of hyaline, amoeboid, intra-cellular bodies, and one segmenting body. The examination was made during the paroxysm. Quinine, five grains every four hours, was begun at 4 p. m. on the 15th, after which date there were no further paroxysms.

The case is of considerable interest on account of the rarity of irregular and remittent fevers in association with tertian infections. The probability is, that we were dealing here with an infection with several groups of the parasite in different stages of development, though it may be that the regular course of the fever was somewhat interrupted by the treatment with cold baths. It is of interest, that at the time when the organisms were discovered, two groups only were found. At this time, however, it will be noted that the temperature, which had previously been irregular, had assumed a more regular course. On the whole, the consideration of the case, and the inspection of the chart, would suggest that the probable course of events had been as follows; primarily, severe infection with multiple groups of the tertian organism, modification of the infection by rest in bed, and the treatment with cold baths, until finally, at the time when a thorough examination of the blood was first made, only the two stronger groups of organisms remained. It will be noted, by consulting the chart, that the paroxysms on the 10th, 12th, and 14th occurred in the morning; while those on the 11th, 13th, and 15th occurred in the afternoon.

In 3 cases there was no fever in the hospital.

In 13 cases with fever on entrance, there was a *spontaneous disappearance* of the fever in the hospital.

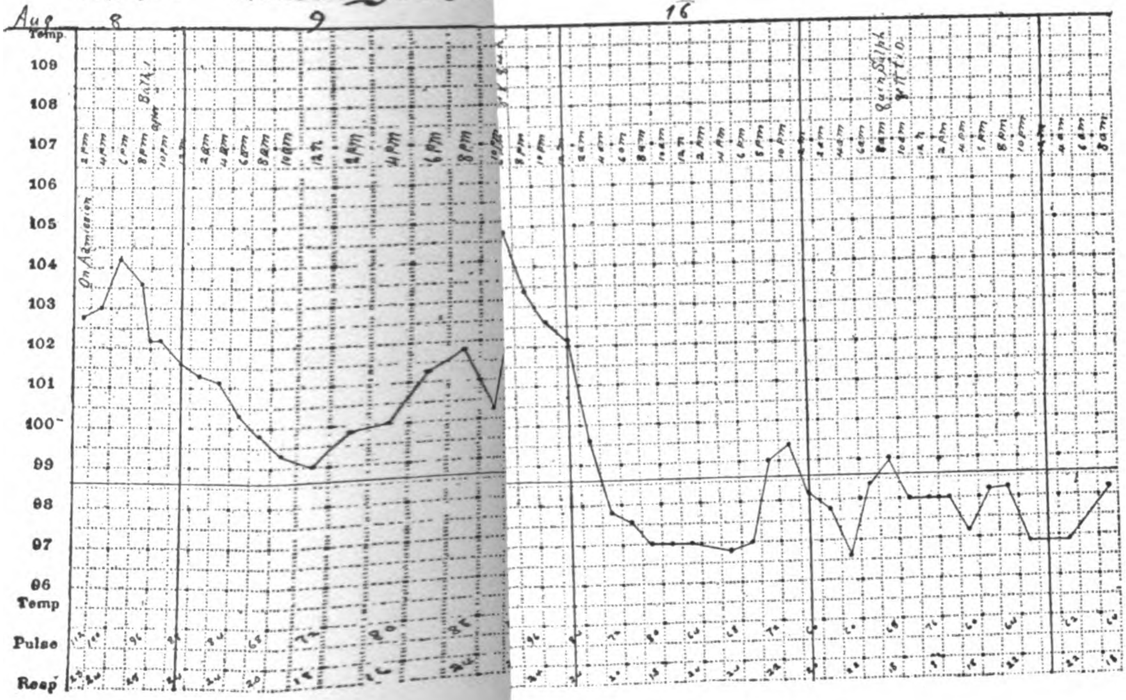
In two of these cases apparent spontaneous recovery was followed later by a relapse, the fever recurring in the first in six, in the latter in three days.

In the 116 cases, there were noted:

Chills in	107
Chilly sensations in	4
Vague general symptoms in	5
	116

One of the instances in which no chill was noted was a child ten months of age.

No. 5703 William Yeckin



The *average duration of the paroxysms* was about eleven hours (10.7).

Organisms.—In all these instances characteristic tertian organisms were seen, arranged distinctly in two groups. In 10 cases flagellate bodies were noted; in 7 instances during the paroxysm; in 2 just before the paroxysm; in 1 between paroxysms when the temperature was normal. In none of these instances had the patients had quinine.

Segmenting bodies were noticed in 42 cases, always during the paroxysm.

Cases of Double Tertian Infection in the Dispensary.—There were 72 cases of double tertian infection treated at the dispensary. Of these, 58 gave a history of having had quotidian *paroxysms*; 8 gave a history of tertian paroxysms, all showing, however, a double set of organisms; 3 cases gave a history of having had tertian paroxysms becoming irregular after quinine; 2 gave a vague uncertain history of quotidian fever; one case had had but one chill, the day before entry.

Of the 58 cases having had characteristic quotidian paroxysms, 14 had had tertian paroxysms at one time or another. Of the cases giving vague uncertain histories, one complained simply of anorexia and vague general pains. The other was a Slav, who was unable to make himself understood, further than that he complained of chills.

In the 72 cases, there was a history of:

Chills in	65	instances.
Chilly sensations in	3	"
Fever only in	1	"
Headache in	1	"
"Paroxysms" in	1	"
No note in	1	"
	72	"

In 5 of the 72 cases, segmenting organisms were noted; in 2, flagellate bodies were seen, in each instance at the time of the paroxysm.

Summary of the Cases of Double Tertian Fever in the Hospital and Dispensary.—There were 188 cases of double tertian infection seen in both hospital and dispensary. Of these, 172 gave a history of having had quotidian *paroxysms*. Thirty-six had had, at one time or another, tertian paroxysms. There were:

Chills in	172	cases.
Chilly sensations in	7	"
No chills in	7	"
"Paroxysms" in	1	"
No note in	1	"
	188	"

Organisms.—Segmenting bodies were noted in 47 instances, always during the paroxysm. Flagellate bodies were noted in 12 instances, in all during or just before the paroxysm, with one exception, where the temperature was normal, between paroxysms.

Cases.

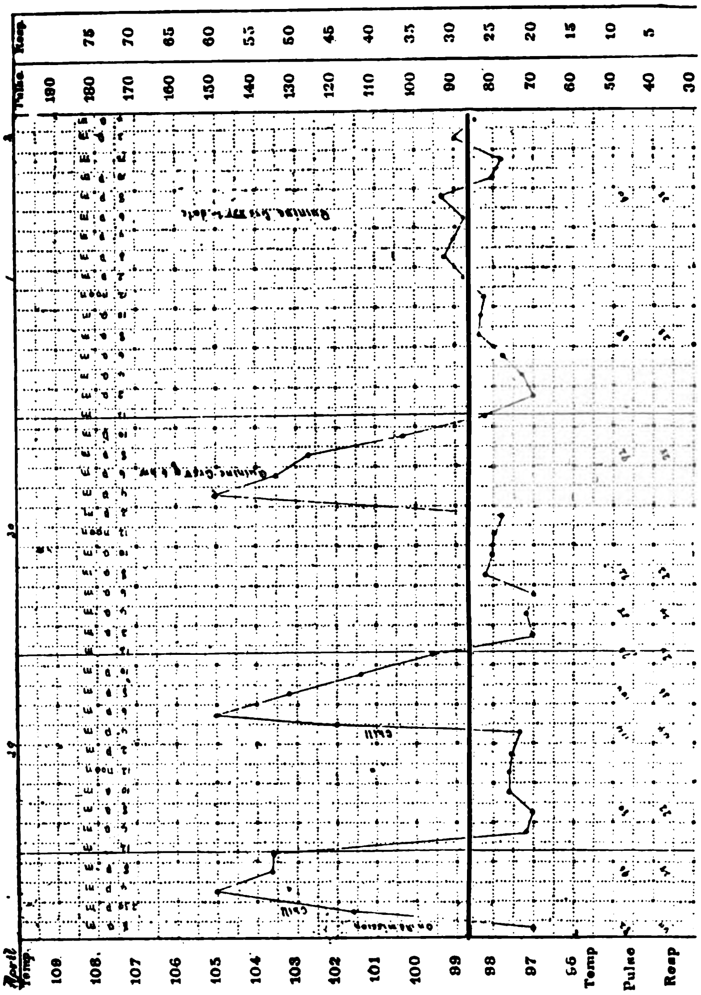
A good example of the double tertian infection is the following:

Case 2998.—J. F., aged 37, German, admitted July 28th, 1891. Has had frequent attacks of malarial fever during the last seven years in Texas; has been in Baltimore seven weeks. About a week ago he began to have chills in the afternoon, which have occurred daily. Temperature on admission 97°. *Physical examination* negative, excepting for the palpable spleen. The *blood* showed typical intra-cellular tertian organisms, full and half grown, and extra-cellular fragmenting forms. The chart shows three characteristic paroxysms.

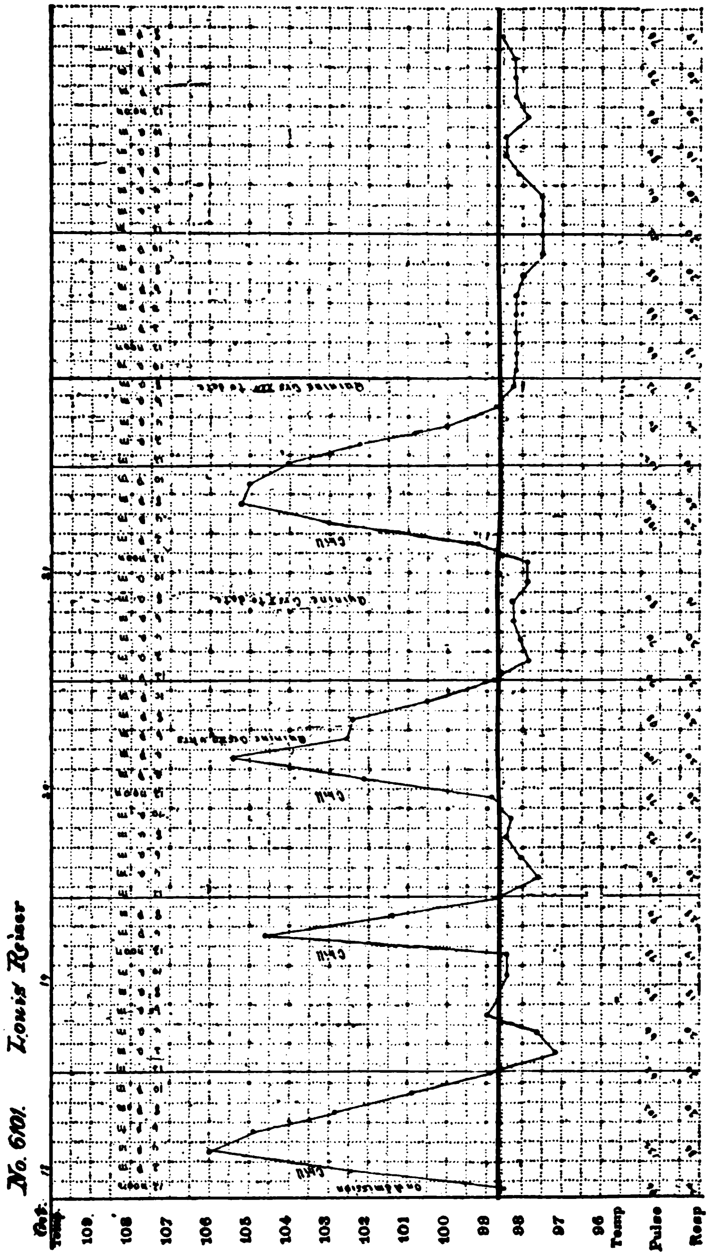
It is interesting to note that the paroxysms on the 28th and 30th began at about 2 p. m., while that on the 29th occurred between 4 and 5 p. m. This point is one of considerable interest, as it serves, sometimes, to demonstrate very clearly the fact that the daily chills depend upon two different sets of organisms. Sometimes it is possible to observe, through a considerable length of time, the regular difference between the time of onset of chills following one another on alternate days, those on the first and third day occurring at one time, while those on the second and fourth occur at another.

Case 6101.—L. R., single, aged 16, native of the United States, admitted October 18th, 1892. The present is his first attack of malarial fever. It began six days ago with creeping chills. Yesterday he had a severe shaking chill. The spleen was readily palpable. The *blood* showed two sets of tertian organisms. The chart in this case shows a regular quotidian intermittent fever, with paroxysms occurring at almost exactly the same hour daily.

The fact that these cases depend on the action of two groups of tertian parasites is demonstrated not only by the examination of the organisms, and by the fact that one may trace in the temperature curve the similarity of the chills on alternate days one with another (hour of onset, severity, duration); it is often possible to demonstrate this point with great clearness by the use of quinine. Golgi has shown



that the parasites are most successfully combated with quinine at the time of segmentation, before the new group of young parasites has entered the red corpuscles. After segmentation, only very large doses of quinine will destroy the organisms. Thus, one dose of quinine,


No. 6101.
Louis Reiser
Oct.
Temp
109
108
107
106
105
104
103
102
101
100
99
98
97
96
Temp
Pulse
Resp
on admission
Chill
Chill
Chill
Chill
Quinine grs x
Quinine grs x to date
Quinine grs XXX to date

given just before or early in the paroxysm, will, at times, almost destroy an entire group of organisms which has reached its perfect development and has begun to segment, while a half-grown set of parasites will continue in its course of development. In this way, then, we should be able to change a quotidian into a tertian malarial fever by the administration of quinine in a single moderate dose before or early in the paroxysm. This is the fact, as may be shown very clearly by the following case. This case was modified experimentally before the ward class.

CASE 9047.—P. D., male, aged 36, German, laborer, admitted May 8th, 1894, complaining of cough, fever, thoracic pains and weakness.

Family and personal history bear no relation to his present trouble, excepting that two years ago he had an attack of chills and fever of unknown type.

Present illness began a week before entry. Chills on the third, on the fifth, sixth and seventh, and also at noon on the day of entry.

Physical examination was negative, excepting for the palpable spleen.

Urine normal. Temperature 103.6° on entry.

8–5–94. *Blood* at 4.15 p. m. showed a number of nearly full-grown typical tertian organisms, a few amoeboid, intra-cellular, hyaline forms, two fragmented extra-cellular bodies, pigmented leucocytes.

9–5–94. A chill being expected, five grains of quinine were given at 11.15 a. m.; chill at 12. The blood at 9 a. m. showed a few large, full-grown, extra-cellular bodies and a number of half-grown forms.

10–5–94. Chill again about eleven o'clock. *Blood* at twelve showed a number of typical segmenting parasites, a few large, full-grown forms, several amoeboid, intra-cellular, hyaline bodies, one large, fragmenting, extra-cellular body, pigmented leucocytes, *no half-grown forms.*

11–5–94. No paroxysm.

12–5–94. Paroxysm about ten o'clock. *Blood* at eleven showed a few segmenting bodies, several full-grown and large fragmenting, extra-cellular forms, no half-grown forms. Quinine gr. X (0.65) at the height of the paroxysm; gr. II (0.13) three times a day afterwards. The organisms disappeared almost immediately afterwards; no further fever.

Surely no better proof than this case could be asked to demonstrate the dependence of these quotidian paroxysms upon a double tertian infection.

The same point is sometimes brought strongly to one's notice in the case of an individual who enters the hospital with one strong and one weaker set of organisms. Placing the patient in bed and upon a good diet is often sufficient to bring about the spontaneous disappearance of one group, so that the quotidian paroxysms are succeeded by tertian fever.

CASE 4889.—C. M., single, aged 34, Pole, admitted March 16th, 1892. Second attack, possibly a relapse of an attack for which he was treated by methylene blue in the hospital. Daily chills for five days.

Patient had paroxysm in the dispensary. The *blood* showed characteristic segmenting bodies of the tertian type, with fifteen or more segments; large, transparent forms, with actively-moving pigment granules; a *very large number of fragmenting, extra-cellular, pigmented forms;* a few half-grown, intra-cellular forms; *no fresh hyaline bodies.*

At 4 p. m., a number of half and nearly full-grown intra-cellular, pigmented forms, fragmenting extra-cellular bodies, *no hyaline bodies.*

17–3–92. Paroxysm at noon.

Blood at 3.45 p. m.; occasional large, full-grown, tertian bodies, a certain number of extra-cellular, fragmented organisms, small, actively amoeboid, hyaline forms, only an occasional half-grown organism.

18–3–92. Temperature normal. An occasional fully-developed, intra-cellular parasite, numerous extra-cellular, fragmenting bodies, no hyaline bodies, a number of half-grown forms.

Paroxysms on the 19th, 21st, 23rd, the *blood* showing characteristic single tertian infection. At 8 p. m. on the 22nd, and 8 a. m. on the 23rd, eight grains of quinine were given, having no influence whatever upon the paroxysm of the 23rd. After this, quinine was given regularly without further fever, the organisms rapidly disappearing.

This case shows, in an interesting manner, the association of large numbers of extra-cellular, fragmenting bodies with the spontaneous disappearance of one group of organisms. It also demonstrates clearly the inefficacy of moderate doses of quinine in preventing a paroxysm, if given when the organisms have already entered into the red corpuscles; the paroxysm on the 23rd, it will be seen, occurred just as if nothing had been done.

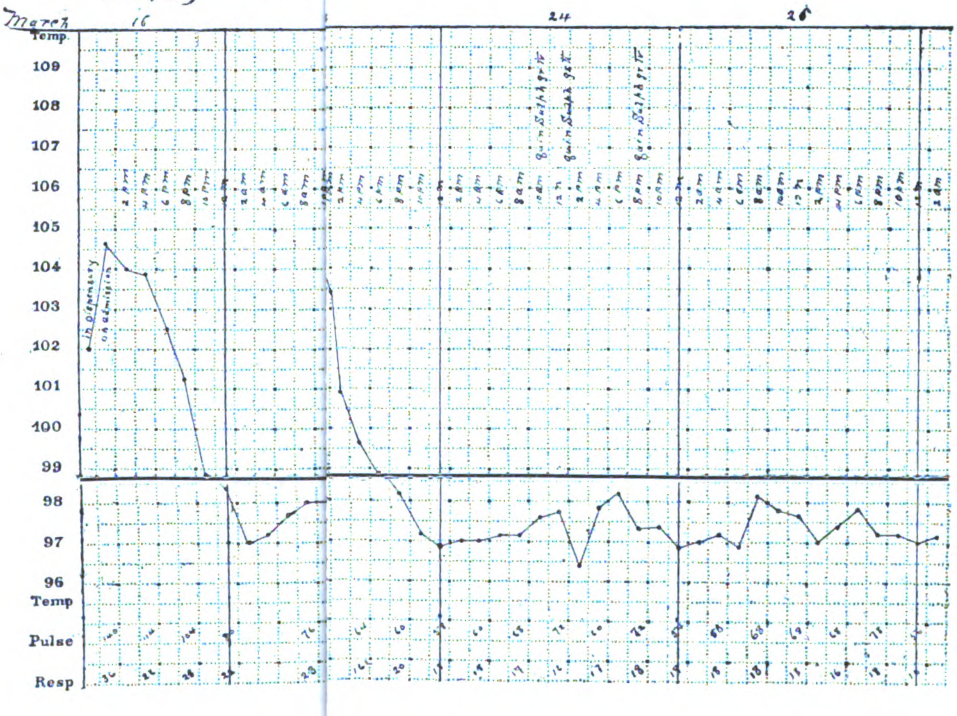
QUARTAN INFECTIONS.

There were five cases of quartan infection, all occurring in the hospital. Of these there were:

(1). Single quartan infection	2
(2). Double " "	0
(3). Triple " "	3
	5

(1). *Single Quartan Infections.*—Of the two cases of single quartan infection, both showed characteristic quartan paroxysms. The paroxysms lasted between 10 and 11 hours (10.6). In both instances there were *chills.*

No. 4889 Cris.



March
16
24
26
Temp.
109
108
107
106
105
104
103
102
101
100
99
98
97
96
Temp
Pulse
Resp
in Germany
on admission
2 pm
4 pm
6 pm
8 pm
10 pm
2 am
4 am
6 am
8 am
10 am
12 m
Quin Sulph gr x
Quin Sulph gr x
Quin Sulph gr x
100
104
76
64
60
60
68
72
60
76
68
68
64
72
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28
28
20
18
17
16
17
18
18
16
15

Organisms.—The organisms in both instances were of the characteristic quartan type described by Golgi. Segmenting bodies were noted in one case; in the other, the examination of the blood was imperfectly made. Flagellate bodies were not seen.

(2). *Double Quartan Infections.*—There were no cases of double quartan infection noted.

(3). *Triple Quartan Infections.*—There were three cases of triple quartan infection admitted to the hospital. Of these, the types of fever were as follows:

Abortive quotidian elevations of temperature	1
Slight quartan paroxysms	1
One paroxysm on day of entry, afterwards normal	1
	3

Chills occurred in all these instances.

The *duration of the paroxysms* averaged about ten hours.

Organisms.—All of the cases showed three groups of characteristic quartan organisms. Segmenting organisms were seen in all cases during the several hours preceding the paroxysms; in several instances they were found as much as eight hours before the paroxysms.

In a number of instances where there were but few parasites, segmenting bodies were seen on days when no paroxysm occurred.

In two cases, flagellate bodies were seen.

Cases of Quartan Fever Occurring in the Hospital.

CASE 1.—L. G., male, sixteen years of age, admitted to hospital November 29th, 1890.

Family history good. Has always been in good health, excepting for an attack of tertian ague in July, 1889. For two weeks he had chills every other day; then a period of rest would follow, lasting two or three weeks. This lasted until October, 1889. After Christmas he had chills off and on until July, 1890. The day before entry he had a chill lasting about half an hour, followed by fever and sweating. Throughout the last year he has taken quinine in broken doses, omitting treatment usually as soon as the chills disappeared. The examination of the *blood* showed "a few intra-cellular organisms, no crescents or flagellate bodies."

The physical examination was negative, excepting for a greatly enlarged spleen. The urine was dark yellow, clear, acid, 1028, no albumen, no casts, no diazo reaction.

At 8 p. m. on the 29th the temperature was 100.5°.

30–11–90. Temperature practically normal throughout the day.

1–12–90. Paroxysm in the afternoon, temperature reaching 104.2° at 4 p. m.

2–12–90. Temperature normal.

3-12-90. Temperature normal.

4-12-90. Chill in the afternoon.

A chill occurred also on the afternoon of the 7th, and on the 10th, the temperature being perfectly normal between.

On the 11th, treatment with one grain of quinine, three times a day, was begun, the temperature remaining quite normal thereafter until the 29th of December, when the patient was discharged, the examination of the blood being negative. The organisms throughout showed rather coarse pigment. On the day of the chill, segmenting bodies were always observed; these bodies were very numerous during the morning hours, from three to six hours before the chill. They were most beautifully symmetrical rosettes, showing, in all instances where the leaflets were counted, from six to eight segments.

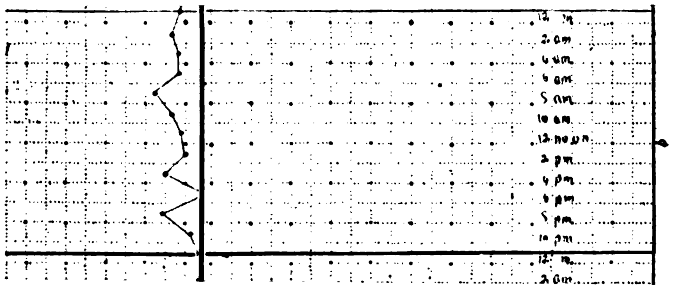
Case 2 (4368).—Male, aged 52, German. The family history was negative; personal history good. Present illness began on the 8th of December, when he had a severe chill, lasting for about an hour, followed by fever and sweating; none on the two following days. The physical examination was negative, excepting for the palpable spleen; the urine was normal. The *blood* showed fairly numerous rounded and ovoid, coarsely pigmented, intra-cellular bodies, which did not quite fill the corpuscle. The markedly greater refraction and the sharper outline of the body, as compared to the ordinary tertian forms, were noted. The amoeboid movements were very slight, and the pigment was almost motionless; in some bodies no motion could be made out. The pigment granules appeared coarser than those in the ordinary tertian form of the parasite, and of a slightly different color. As the chart shows, the patient had two paroxysms, four days apart. The examination of the blood was, however, not carefully made at the time of the paroxysms, and segmenting bodies were not noted. The fully-developed organisms, however, were not as large as those in ordinary tertian fever. On the 15th of December methylene blue, 0.1 four times a day, was ordered. No organisms were seen after the 18th. There were no further attacks of fever. The patient died of an attack of influenza, with extensive broncho-pneumonia, on the 9th of January.

Case 3 (9773).—J. S., single, aged 10, Pole, admitted April 30th, 1894. She speaks but little English, and the history is not satisfactory. Chills and fever last fall; also two months ago. For two or three weeks chills at uncertain intervals.

On entry, 8 p. m., the *blood* showed one half-grown intra-cellular body, with a small amount of very dark pigment which was rather larger than that seen in tertian parasites, and very slightly motile, while the body was round and scarcely at all amoeboid; several fragmented, extra-cellular parasites.

1-5-94. Physical examination negative, excepting for the palpable spleen.

Blood, 9 a. m. A few organisms seen this morning, nearly filling up the body of the corpuscles. These corpuscles are not expanded, as one ordinarily sees in tertian infection; on the other hand, they appear to be rather smaller than the others about them, as if contracted about the body. The pigment is rather dark and coarse. The movements of the pigment granules are slow, while the surrounding protoplasm is quite refractive. One form, which was slightly elliptical in shape, a little smaller than an ordinary red corpuscle, with almost non-motile, black pigment, showed a


12 m.
2 am.
4 am.
6 am.
8 am.
10 am.
12 noon
2 pm.
4 pm.
6 pm.
8 pm.
10 pm.
12 m.
2 am.

suggestion of a double contour; it was very similar to the ovoid aestivo-autumnal forms in appearance, except for the irregular arrangement and the quantity of pigment. A number of fragmenting and vacuolating, extra-cellular forms, and several bodies nearly, but not quite filling up the red corpuscle, with almost non-motile pigment and quite refractive protoplasm, were seen; also other smaller bodies, about one-third the size of a corpuscle, quite refractive, with very slow amoeboid movements and slightly motile pigment granules. Several early segmenting forms were found.

At 2 p. m. a number of characteristic segmenting bodies, with from six to ten segments, were seen. Paroxysm in the afternoon. During and just after the paroxysm, small, amoeboid, intra-cellular forms were seen.

2-5-94. Temperature, at 8 p. m., 100.1°.

3-5-94. Temperature normal.

4-5-94. Temperature 100.5° at 8 p. m.

7-5-94. Temperature 99.8° at 8 p. m.

10-5-94. Temperature 99.8° at twelve, midnight.

13-5-94. Temperature 101.5° at 8 p. m.

Examination of the *blood* revealed a characteristic triple quartan infection, segmenting bodies being observed during the first four days, notwithstanding the slight rises in temperature. The strongest group of organisms reached maturity on the 1st, 4th, 7th, 10th, and 13th, causing slight abortive paroxysms. The patient was removed from the hospital by her parents on the 13th, when she was given a prescription for quinine.

CASE 4 (10429).—A. K., single, aged 12, Pole, entered the hospital on July 19th, 1894. Does not speak English; history imperfect.

20-7-94. Examination of the *blood*, at 12 m., showed typical quartan organisms, a number of early segmenting forms, other small bodies just beginning to develop pigment, other more advanced bodies nearly filling up the shrunken, brassy-colored corpuscle, a few extra-cellular, fragmenting bodies; one small pigmented form was seen to burst from the corpuscle which became immediately decolorized; the escaped parasite became immediately deformed. Temperature, at 6 p. m., 99.6°.

21-7-94. Temperature subnormal during the night; 100.6° at 8 p. m.

Blood, 2 p. m., showed a few segmenting bodies.

9 p. m.; a number of characteristic quartan organisms, nearly filling the shrunken corpuscle, with almost immobile pigment; a few hyaline, amoeboid, non-pigmented forms.

22-7-94. Temperature subnormal during the night; 99.2° at 8 p. m.

Blood, 3 p. m. A few intra-cellular, hyaline bodies, one or two larger pigmented bodies, several nearly full-grown pigmented bodies, large and fragmented extra-cellular bodies with active pigment granules, pigmented leucocytes.

23-7-94. Temperature subnormal during the night; 99° at 10 a. m., 2 p. m. and 8 p. m.

Examination of the *blood* unfortunately not noted.

24-7-94. Temperature subnormal during the night; 103.8° at 6 p. m., to-day.

Blood at noon showed segmenting bodies.

8 p. m.; a few intra-cellular, apparently half-grown and some nearly full-grown bodies, several swollen, extra-cellular forms with active pigment, one flagellate body.

25-7-94. Quinine, two grains (0.13) every four hours. Temperature normal on the 26th. Slight paroxysm on the 27th and 28th. Normal on the 29th and 30th, when the patient was discharged with quinine. The organisms were present in the blood until the day of discharge. On that date none were to be seen.

The case was one of typical triple quartan infection, the organisms showing characteristics entirely different from those of the tertian parasite. It is interesting to note how, with the abortive paroxysms, the whole life history of the parasite could be traced in the circulating blood. The inefficacy of the quinine in stopping the paroxysms on the 27th and 28th is what might have been expected, the administration of the drug having been begun when the parasites had already entered the corpuscles.

Case 5 (10431).—19-7-94. A. K., single, aged 15, Pole, complains of chills and fever; no further history obtainable. Is a sister of the last patient.

Physical examination negative, excepting for the palpable spleen.

Temperature 102.2° at 8 p. m.; no marked paroxysms after this, though slight rises in temperature were noted on the 25th and 28th. Quinine begun on the 25th.

Examination of the blood showed a dying out triple quartan infection. Flagellate bodies noted on the evening of the 23rd. Segmenting bodies were observed on the day of entry and on several other occasions, notwithstanding the slight abortive rises of temperature.

It is interesting to note that, in these dying out quartan infections, we observed, as has Antolisei, extra-cellular forms with active pigment granules, fragmenting forms, and flagellate bodies, just as we have noted in tertian fever. The large, extra-cellular forms, however, are materially smaller than those of the tertian variety; they are not as frequent; they are not as transparent; the pigment is larger and coarser. There was no question in any of these cases of a combined infection, not an organism having been observed which was not quite distinctively of the quartan type.

A sixth case may probably be added to those above mentioned:

A girl, aged 15, a German, was admitted to the hospital on the 26th of January, 1892. The family history was negative. She had never had previous illnesses, excepting two years before, when she had malarial fever of unknown type The illness of which she then complained began in August with chills which occurred, she said, about twice a week. At times she did not have regular chills, but "felt badly." This continued until October, when regular chills began, which were stopped by quinine. After two weeks the chills recurred, and for the past two weeks patient had had a chill every fourth night, the chill, associated with severe headache, lasting an hour. This was followed by fever and sweating. Bowels regular. The physical examination was negative, excepting for the palpable spleen. The patient showed no paroxysms in the hospital. She had had quinine outside before entrance. The blood showed a very few organisms similar to those observed in the other quartan cases, but, owing to the imperfect entry made concerning them, we have not felt justified in including this case among those where the type was definitely made out. We have little doubt, however, that this also represented a case of quartan malaria.

Æstivo-autumnal Infections.

There were in all 189 cases of aestivo-autumnal fever observed in the hospital and dispensary. Of these, 105 cases were treated in the hospital, and 84 in the dispensary.

Cases of Aestivo-autumnal Infection Observed in the Hospital.

In the 105 cases of aestivo-autumnal infection observed in the hospital, one of which was the relapse from a case previously treated, the types of fever may be divided as follows:

Quotidian intermittent paroxysms	38[*]
Daily paroxysms, with a tendency to become continuous	16[†]
Continuous fever, with quotidian exacerbations	13
Tertian intermittent paroxysms	6
Continuous fever, with no sharp paroxysms	9
Normal or subnormal temperature	8
Moderate irregular fever	8
Indefinite	7[‡]
	105

Thirteen of these cases which did not show tertian fever in the house gave a history of having had tertian paroxysms before entrance.

Thus, of the 105 cases, only 38 showed sharp quotidian intermittent paroxysms, though 67, or not quite two-thirds, showed a distinct tendency toward quotidian exacerbations. Six showed tertian paroxysms, while 20 gave a history of having had tertian paroxysms at some time. On the other hand, 38, or more than one-third of all the cases, showed a more or less continuous fever.

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[*] In several instances the patient was admitted during the paroxysm, and showed only one or more slight daily rises of temperature on the following days, with a normal temperature afterwards; so clear a history was, however, given of sharp paroxysms before entering the hospital that the cases were placed in this list.

[†] Under this heading are classed those cases which showed several distinct paroxysms, where, on one or more instances, the temperature failed to reach the normal point before the beginning of the following paroxysm, "subintrant fever."

[‡] Cases showing but one paroxysm in the house, with a vague, indefinite history.

Of these 105 cases, 68 either showed, in the hospital, or gave a clear history of having had, before entrance, distinct *chills*, and 7 chilly sensations; 30 complained only of headache, pains in the back and limbs, etc., the symptoms ordinarily accompanying an acute infection.

The *duration of the paroxysms* in these cases differed considerably from those in the tertian and quartan infections, averaging between twenty and twenty-one hours, while in the tertian and quartan fever it averaged from ten to twelve hours. In many instances the paroxysm lasted considerably longer—in one case, for instance, for thirty-eight hours, while in a number of instances long paroxysms which would probably have brought up the average duration considerably, could they have been reckoned among those on which this calculation is based, were followed by a second paroxysm before the fall to normal occurred ("subintrant" cases), so that the length of each paroxysm could not be estimated. It will also be noted that, while in 97.2 per cent. of the cases of tertian and quartan infection in the hospital, chills or chilly sensations were present, in only 71.4 per cent. of the cases of aestivo-autumnal fever were these symptoms noted.

While in some cases with quotidian paroxysms the periods of subnormal temperature during the attacks were similar to those observed in double tertian fever, there were many instances where the overlapping of paroxysms caused a continuous fever, thus showing a chart quite different from that observed in the common double tertian intermittent. In some cases a continuous elevation of temperature, most suggestive of typhoid fever, was noted. In 5 cases where there was fever on admission, the temperature disappeared spontaneously.

Organisms.—These 105 cases all showed the presence of the organisms characteristic of aestivo-autumnal infection. In all the cases in which fever was present during the stay in the hospital, the small, hyaline, ring-shaped and often actively amoeboid bodies described in an earlier section were noted. In several of the cases where no fever was present, only the crescentic and ovoid bodies were found.

In 35 cases, only these small, hyaline bodies, with or without a few minute granules of pigment, were seen. Of these, 27 were primary attacks, 8 were repeated attacks or relapses.

In 70 cases ovoid and crescentic bodies were found. Of these cases, 46 were primary attacks, 24 were repeated attacks or relapses. In 5 cases nothing was found in the blood on admission, while later ovoid and crescentic forms were seen.

In 29 cases hyaline bodies alone were present on admission, ovoid and crescentic forms appearing later. Of these 29 cases in which hyaline bodies alone were found on admission, with the development of the crescents later, the crescentic forms appeared before the beginning of treatment in 11 instances, while in 18 cases the treatment had been begun previously. In these 18 cases, the treatment was begun in the first week in only 4 instances.

Of the 70 cases in which crescentic and ovoid bodies were seen, in only two instances were these bodies noted before the eighth day of the disease. The first case was that of a man who had had previous attacks, and had been living in Jamaica, having left for Baltimore two weeks before entering the hospital. He dated his symptoms, however, but two days back. It is highly probable that in this case the disease had lasted longer than the patient fancied, the crescents being the remnants of a previous attack, from which complete recovery had never occurred. The second case was a patient who had recently arrived from Cuba. He dated his quotidian chills, fever and delirium but five days back. It is somewhat striking that both of these patients had been living in the tropics, and that one had had already several previous attacks. In 28 of these 70 cases the crescents were noted before the fourteenth day. In all the remaining cases the patients had been ill at least two weeks.

In 5 cases the patients had taken quinine from five to nine days before the appearance of crescents.

Hyaline amoeboid bodies were found alone on entrance in 64 instances. In 29 of these instances crescents appeared later; while in 35, hyaline bodies alone were seen throughout.

Of the 35 cases in which hyaline bodies alone were seen, in one case the disappearance of the organisms before the beginning of quinine is noted. Case 8268 entered on the fifth day; no organisms were seen after the sixth; quinine given on the 14th day. It should be said, however, with regard to this case, that the discovery of hyaline forms is so delicate a matter that it is not impossible that a more careful, continued search would have shown these bodies.

Out of the 35 cases where hyaline bodies alone were seen, 19, or about one-half, lasted over two weeks before the disappearance of the organisms; 16 lasted over twenty days. In two of these 16 cases there is considerable probability that the real attack may have been of much shorter duration than would appear from the history. With the exception of these two cases, the longest period during which symptoms existed, with the presence of hyaline bodies alone in the blood, occurred in case 6289, where the duration of the case was from eight to nine weeks, and in case 8105 which lasted six weeks. Of the 19 cases, where hyaline bodies existed alone for more than two weeks after the onset, 15 were first attacks.

Of the 35 cases, in 17, treatment was begun in the first week; in 3 in the second. In 2, the duration of the case was not known, while in 13, with the exception of two cases in the tenth week, treatment was begun all the way from the third to the ninth week; in 2 instances, as noted above, the cases had existed from nine months to a year.

Out of 64 cases, where hyaline bodies alone were present on admission, in 21, treatment was begun in the first week, crescents appearing in only 4, or 19 per cent.; in 8, in the second week, crescents appearing in 5, or 62.5 per cent.; in 35, where the treatment was begun after the second week, the crescents appeared in 20 instances, or 57.1 per cent.

In these 105 cases, flagellate bodies were noted in 18. In 6 of these cases quinine had been previously administered; in one case there was some question as to whether the patient had, or had not had quinine. In 10 instances these bodies appeared before quinine was given. The earliest period at which they were noted was on the eighth day. They were, in all instances, associated with the presence of crescentic, ovoid, and round bodies. In 9 of the 18 cases the temperature was normal at the time when the flagellate bodies were found; in 4, they were found during the paroxysm; in 3, during the mild continuous fever; in one instance they were found after death in the spleen. In one case in which the organisms were found during the paroxysm, early in the course, they were found again five days later, when the temperature was normal, after the administration of quinine. In another case they were found, first, ten days after the administration of quinine, and nine days after the temperature was normal; they remained present here till the thirteenth day.

Cases of Aestivo-autumnal Infection observed in the Out-patient Department.—There were 84 cases of aestivo-autumnal fever observed in the dispensary. There were:

Quotidian paroxysms in	35
Tertian paroxysms in	7
"Paroxysms" in	5
Irregular paroxysms in	8
Vague general complaints in	29*
	84

Of the 29 cases complaining of vague general symptoms, one complained of tertian paroxysms, but stated that he believed his fever had been continuous. Of the cases showing quotidian paroxysms, nine had, at one time or another, had tertian attacks.

In only 59 cases were *chills* or chilly sensations noted.

Organisms.—Among the 84 cases, crescentic and ovoid forms were found in 35 instances; of these, 25 were first attacks; 5 were repeated attacks or relapses; 5 were uncertain, probably relapses.

Hyaline bodies alone were noted in 49 instances; of these, 35 were first attacks; 13 were repeated attacks or relapses; 1 was uncertain.

Of the 84 cases, 21 were seen during the first week, and of these only 3 (14.2 per cent.) showed crescents. In two of these cases they were noted on the seventh, and in one on what the patient believed to have been only the fourth day of his disease. 15 cases were seen in the second week, and in only 3 of these (20 per cent.) were crescents found. 46 cases were seen after the second week, and in 27 (58.6 per cent.) of these, crescents were seen. Out of 33 cases admitted or seen later than the third week, crescents were found in 20 (60.6 per cent.). Of 2 cases, where the duration of the disease was doubtful, crescents were seen in one.

Of the 13 instances in which hyaline bodies alone were found after the third week, in 3 the patients had had quinine before, with a temporary relief of the symptoms. In 4 of the instances where crescents were found, quinine had been administered before their appearance.

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* Headache, pain in the back and limbs, and the symptoms generally associated with acute infections.

Flagellate bodies were noted in two instances, on both occasions after the administration of quinine and during normal temperature.

Cases of Aestivo-autumnal Infection in the Hospital and Out-patient Department.—There were 189 cases which showed the organisms characteristic of aestivo-autumnal fever. One was a relapse of an attack previously included in the classification. If we combine the observations of the temperature in those cases which were in the hospital with the most reasonable deductions that may be drawn from the statements of the out-patients concerning their attacks, we obtain the following result:

Quotidian intermittent fever	73	cases.
Tertian fever	13	"
Continued fever, generally associated with daily paroxysms	66	"
Moderate irregular fever	21	"
Normal or subnormal temperature	8	"
Indefinite	8	"
	189	

Organisms.—In 117 cases there were *chills;* in 17 chilly sensations; in 55 vague general symptoms only.

In the 189 cases of aestivo-autumnal fever seen in the hospital and out-patient department,

Hyaline bodies alone were found in 84. Of these there were:

Primary attacks	62
Relapses or repeated attacks	21
Uncertain	1
	84

Crescentic bodies were found in 105. Of these there were:

Primary attacks	71
Relapses or repeated attacks	29
Uncertain	5
	105

The following table shows, graphically, the time at which crescents generally developed in the hospital, and, so far as could be made out, in the dispensary cases.

1st week: Admitted to Hospital.........	36;	crescents 2	
" " Dispensary......	21;	crescents 3	
	57	5	8.8 per cent.*
2d week: Cases admitted to the Hospital, or present without having previously shown crescents.........	35;	crescents 27	
Cases consulting at Dispensary..........	15;	crescents 4	
	50	31	62 per cent.
After the second week: Cases admitted to the Hospital, or still remaining, without having shown crescents...	48;	crescents 35	
Cases in Dispensary.........................	46;	crescents 26	
	94	61	64.8 per cent.
Cases of doubtful duration: House.......	8;	crescents 5	
Dispensary.	2;	crescents 2	
	10	7	70 per cent.
Relapses, House..............................	1;	crescents 1	100 per cent.

Actual advanced segmenting bodies were never seen in the circulating blood, though forms with a central pigment block were noted in a number of instances.

Flagellate bodies were seen in 20 cases.

In 8 cases quinine had been previously administered.

In 1 case they were found both before and after the administration of quinine.

In 11 cases the temperature was normal at the time when the flagellate bodies were noted.

In 4 cases the bodies were found during paroxysms.

In 3 cases the bodies were found during mild continuous fever.

In 1 case the bodies were found first during a paroxysm, and again, five days later, when the temperature was normal, following quinine.

In 1 case they were found in the spleen after death.

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* This rather high percentage is explained by the fact that of the two cases showing crescents in the hospital during the first week, one, as has been stated, had had numerous previous attacks, so that it is uncertain as to whether the case may not have been a relapse, while the other came from a most malarious district (Cuba) and had probably had his disease longer than he stated—five days. Of the three cases in the out-patient department, the crescentic bodies were noted on the 7th day in two, while in the other the patient asserted that it was but the 4th day of the disease.

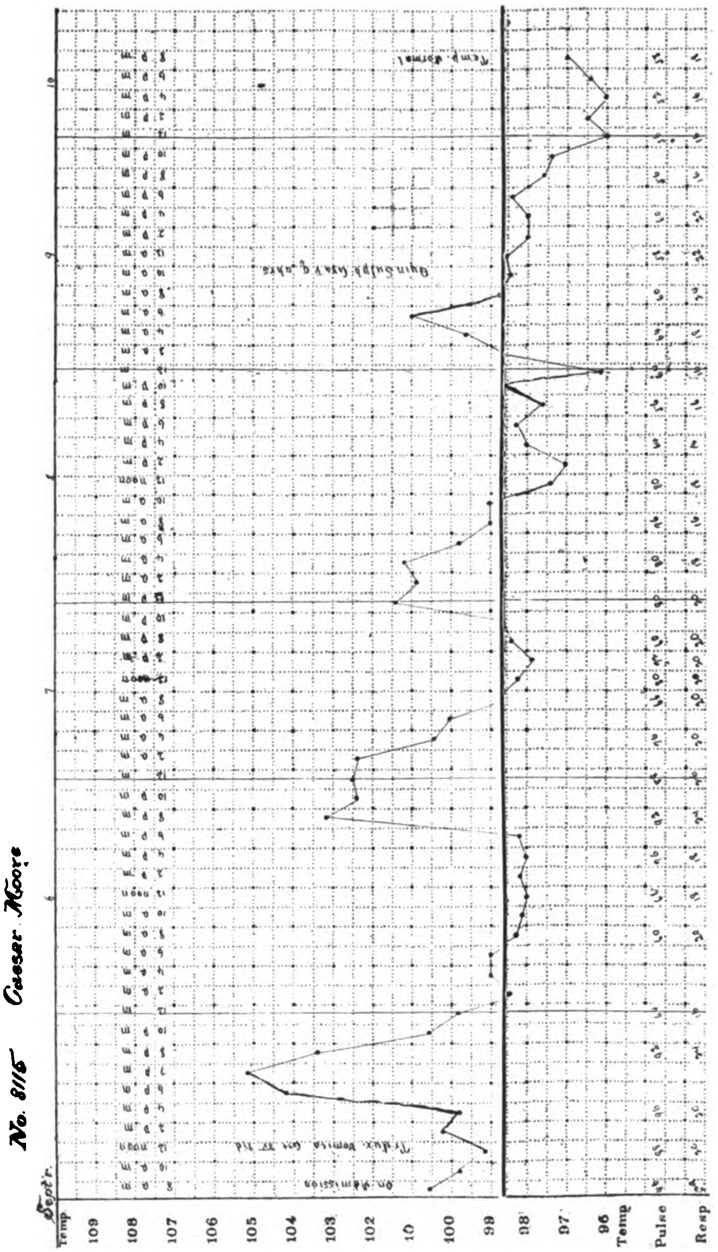
Cases.

The following cases will serve to illustrate some of the different varieties of fever which were found associated with aestivo-autumnal organisms. The first case shows a chart very similar to that of ordinary double tertian or triple quartan fever.

CASE 8115.—Patient, a man aged 24, colored, entered the hospital at 8 a. m., September 5, 1893. He had had previous attacks of malarial fever, the last attack a year ago; had been ill seven days with headache, general depression, anorexia; no chills, no vomiting, no marked sweating, no nose bleed; has taken no medicine. On the day before entrance, the sixth day after the beginning of the symptoms, the *blood* showed fairly numerous intra-cellular, non-pigmented, hyaline, malarial organisms, small, many of them ring-shaped with sharp outlines. The temperature on entrance was 100.5°. Physical examination was practically negative, excepting for herpes at the corner of the mouth, and a palpable spleen. The urine showed a faint trace of albumen; no casts. The course of the temperature is shown in the chart. The paroxysms were fairly sharp in onset, and associated with chilly sensations, though there were no actual shaking chills. For the first four days only small, hyaline, ring-shaped and amoeboid bodies were seen, which showed, between the paroxysms, one or two very fine pigment granules. Just before and during the early part of the paroxysms the organisms were very scanty in the peripheral circulation, a note having been made on the afternoon of the sixth that no organisms were to be seen at all. The forms seen shortly after the paroxysms were always free from pigment. No segmenting bodies were seen at any time. On the ninth, for the first time, one pigmented crescent was seen, and after this the crescentic and ovoid bodies became very numerous. On the tenth, flagellate bodies were seen for the first time, and while, after the beginning of quinine on the ninth, the small, hyaline forms disappeared with great rapidity, and the temperature returned to normal, the ovoid, crescentic and flagellate bodies were found continually, in considerable numbers, up to the date of discharge, the 14th.

In this case, it will be seen that the paroxysms were very similar to those observed in the ordinary spring tertian fever. There was a tendency towards spontaneous recovery, and the administration of quinine was followed by the immediate disappearance of the fever. The examination of the blood suggested that this was a case of true quotidian malaria, only one set of organisms, apparently, being present.

CASE 7767.—G. E., single, white, aged 29, ship carpenter, admitted to the hospital July 22nd, 1893. Was in the hospital last year, during the latter part of August, with double tertian fever. He has been well since September, 1893. Three days ago he started to work in the morning, when he was seized with an intense frontal headache, anorexia, fever and sweating; the next day he had a


No. 8115
Caesar Moore
Sept'r.
Temp
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107
106
105
104
103
102
101
100
99
98
97
96
Temp
Pulse
Resp
On Admission
Temp. Normal

"dumb chill." To-day, has had a shaking chill lasting forty-five minutes, accompanied by vomiting; complains of constipation. The patient entered at 7.30 p. m. with a temperature of 104.6°. The physical examination was negative, excepting for the considerably enlarged spleen. The urine showed a trace of albumen; no casts were found. The entry on the morning of the 23rd is as follows: "Last night, at 8 p. m., the *blood* contained a very considerable number of the smallest variety of hyaline bodies, some of them homogeneous in appearance, others more or less ring-shaped, some of them amoeboid; no other organisms found. There was no leucocytosis; indeed, rather a small number appeared to be present." The following morning the bodies were less numerous, a trifle larger, and some contained a few fine pigment granules lying at the periphery of the body.

July 23rd, 3.30 p. m., the *blood* showed relatively few organisms. Those which were found were for the most part small, hyaline discs, some of which showed one or two extremely minute particles of pigment at the periphery. 4.15 p. m., temperature about 103°; the *blood* from the spleen showed a number of pigment clumps, which appeared to be free. Many others contained in large mononuclear, colorless cells. There was a considerable number of apparently free organisms a little larger, or about the size of the bodies with central pigment clumps, which were filled with very active, brown pigment granules. They resembled the extra-cellular pigmented forms seen in the spring tertians, excepting for the greater abundance and activity of the pigment. A number of apparently free bodies were seen; some others within red corpuscles, in which there was a small central pigment clump, the surrounding protoplasm being somewhat granular in appearance, with a slightly "scalloped" outline. These were probably early segmenting forms. 11 p. m.; more of the smaller, hyaline bodies present, but still forms with occasional pigment granules.

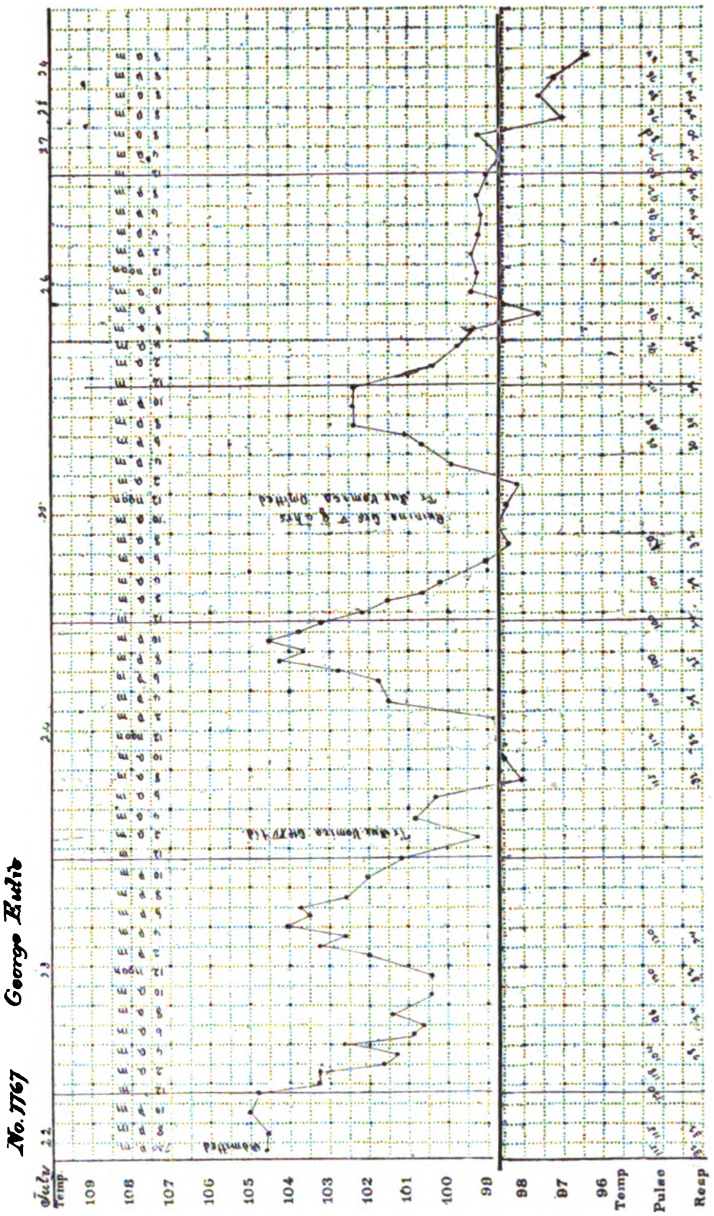
July 24th; in the morning, a majority of the organisms had one or two fine pigment granules. At 11 p. m., at the beginning of the decline of the fever, the blood showed only a few organisms; none were seen which contained pigment.

25-7-93. 10.30 a. m. Hyaline forms are rather larger, and about one-third contain a few fine pigment granules in the periphery. Several similar bodies, extra-cellular, hyaline, rather refractive, with a few granules grouped in the centre. Quinine, five grains (0.325) every four hours.

27-7-93. 10.15 a. m. The blood showed a few organisms, one or two ring-like forms, a few larger amoeboid; no pigmented forms were seen. The temperature, as the chart shows, was normal after the 25th.

In this case, it is seen that two paroxysms overlapped one another, the fever having been continuous for thirty-seven hours after entry. The paroxysms occurring in the house were wholly unassociated with chills. The impression that one obtained from the examination of the blood was that there was but one main group of organisms, though all pigmented forms did not, always, disappear with the paroxysms.

CASE 8024.—E. B., female, single, aged 13, admittted to the hospital on the 24th of August, 1893. This was the first attack of malarial fever. It began about ten days before entry with abdominal pain and diarrhoea which has continued until


No. 1767
George Ellis
July
22
23
24
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28
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Temp
109
108
107
106
105
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103
102
101
100
99
98
97
96
Temp
Pulse
Resp
Admitted
Tr. Nux Vomica. Gtt XV t.i.d.
Quinine Sulp. gr. x q. 3 hrs
Tr. Nux Vomica Omitted

the day of entry. She complains now of pain in the left side, slight cough, considerable headache, anorexia, no chills. The child was well-formed and nourished; lips and mucous membranes of good color; tongue coated; pulse dicrotic; marked typhoidal appearance. Thorax negative; hepatic border just palpable; splenic border to be felt 5½ cm. below the costal margin. Abdomen negative on palpation, not distended, no rose spots. Examination (rather hasty) of the *blood* on the afternoon of the 23d, and at 8.30 p. m., showed no malarial organisms, no pigment-containing leucocytes; a distinct increase in the large mononuclear leucocytes,—five out of twenty-five. The appearance of the child was characteristically typhoidal, and sponge baths were ordered, and continued for twenty four hours. The irregular, continued course of the temperature is shown by the chart, no distinct paroxysms occurring while the patient was in the hospital; no chills at any time during the course of the fever.

On the 26th, for the first time, the examination of the blood showed small, amoeboid, and ring-shaped hyaline bodies.

On the 27th, the fourteenth day of the disease, beside the hyaline bodies, crescentic forms were noted. The hyaline bodies, at 10.20 a. m., when the temperature was 101.8°, contained no pigment. At 7.30 p. m., the temperature 103.8°, the *blood* showed numerous hyaline bodies a trifle larger than in the morning, some with a few pigment granules at the periphery, one larger body with a few pigment granules collected in the centre. At 8.30 p. m., several more bodies with small central collections of pigment granules were to be seen. A number of the organisms were contained in crumpled, refractive, brassy-colored corpuscles; the hyaline bodies were mostly of medium size, a number with a few pigment granules; one free ovoid body; pigmented leucocytes.

28–8–93. 11 a. m. Temperature 100.4°. Organisms perhaps a trifle smaller than last night; very few forms with pigment; one ovoid, refractive, pigmented body. At 3 p. m., the temperature 100.2°, very few organisms; only a few amoeboid and non-pigmented forms were seen.

℞. Quinine, gr. v (0.325) every four hours.

29–8–93. Temperature nearly normal; a few hyaline bodies, and several ovoids and crescents were seen. The hyaline bodies disappeared rapidly, though the crescents remained for some time, none, however, being seen on discharge, 19th of September.

This is a fairly good example of continued fever. There were no sharp paroxysms in the house, though there were slight rises daily. It would seem quite impossible to say whether we were dealing in this case with one group of organisms with overlapping paroxysms,* or with an infection with organisms in different stages of development, where, perhaps, different groups were segmenting through consider-

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* If so, should it be interpreted as a quotidian case, or, perhaps, as a tertian, showing two long paroxysms, beginning respectively on the 24th and 25th? The examination of the blood, in view of the few stages of development which we see circulating, is insufficient to clear up this point.

able periods of time. The first crescents were seen here on about the fourteenth day.

Case 10480.—F. P., female, aged 28, German, admitted 25–7–94, complaining of headache and pain in the back and limbs.

Family history negative. Personal history bears no relation to her present trouble.

The present illness, her first attack, began two weeks before entry with severe headache, a feeling of giddiness, aching pains in the back and limbs, anorexia, occasional vomiting; bowels regular.

On July 20th, had chilly sensations, lasting for about half an hour to an hour, followed by fever and profuse sweating; no nose bleed.

25–7–94. Temperature on entry 98°; 100.7° at 8 p. m.; 101.8° at 10 p. m.

Blood at 8 p. m.: Numerous actively amoeboid hyaline bodies, some containing one or two minute pigment granules, also numerous ring- and disc-shaped bodies.

Urine; dark amber, hazy, acid, 1013, faint trace of albumen, no sugar; diazo reaction present. Microscopically; epithelial cells and leucocytes; no casts found.

26–7–94. Temperature remains elevated. "Patient is in bed, on her back; tongue clean; pupils equal, respond to light and accommodation; lips and mucous membranes of good color; no herpes; pulse full, regular in force and rhythm, rather soft, 96, no thickening of the vessels. Thorax; well formed, costal angle wide, expansion good; fronts, axillae and back clear on percussion and auscultation.

Heart. Position, area of dulness, and sounds normal. Border of the liver not palpable; right kidney just palpable; splenic dulness obliterated by abdominal tympany; border is not felt.

Abdomen, not distended, generally tympanitic, negative on palpation. No rose spots, no glandular enlargements.

Blood, 2 p. m. Large numbers of hyaline bodies, many actively amoeboid, some ring-shaped, a few showing pigment granules.

8 p. m. A few hyaline and ring-shaped bodies.

27–7–94. Temperature remains elevated, no sharp paroxysms.

Blood, 9.30 a. m. Numerous, rather large, hyaline bodies, about a quarter the diameter of a red corpuscle.

2 p. m. A number of smaller bodies, some actively amoeboid, some showing occasional pigment granules. 8 p. m.; a few actively amoeboid hyaline bodies.

28–7–94. Patient is dull and drowsy; temperature remains elevated. The blood at 9 a. m. showed a few hyaline forms. At 3 p. m., negative; at 8 p. m., negative.

℞. Quinine, gr. v (0.325) every four hours.

29–7–94. Temperature has remained continuously elevated since entrance, the course much resembling typhoid fever. Patient has the same dull look, the same dry coated tongue.

Blood, 10 a. m. One amoeboid, hyaline body, several pigmented leucocytes.

3 p. m. Two crescentic, pigmented bodies, several pigmented leucocytes.

8 p. m. One hyaline body with a few pigmented granules, one crescent.

30–7–94. The temperature has remained elevated and uninfluenced by quinine; spleen not palpable; no rose spots.

Blood, 8.45 a. m. Several ring-like bodies; a few hyaline, amoeboid forms, one containing pigment; one large, ovoid, pigmented body.

2 p. m. Negative.

8 p. m. Several crescentic bodies.

31–7–94. Temperature has been steadily falling since the 29th; no great change in the condition. This afternoon the left parotid gland is very tender, and somewhat swollen; temperature at 8 p. m., 101.6°.

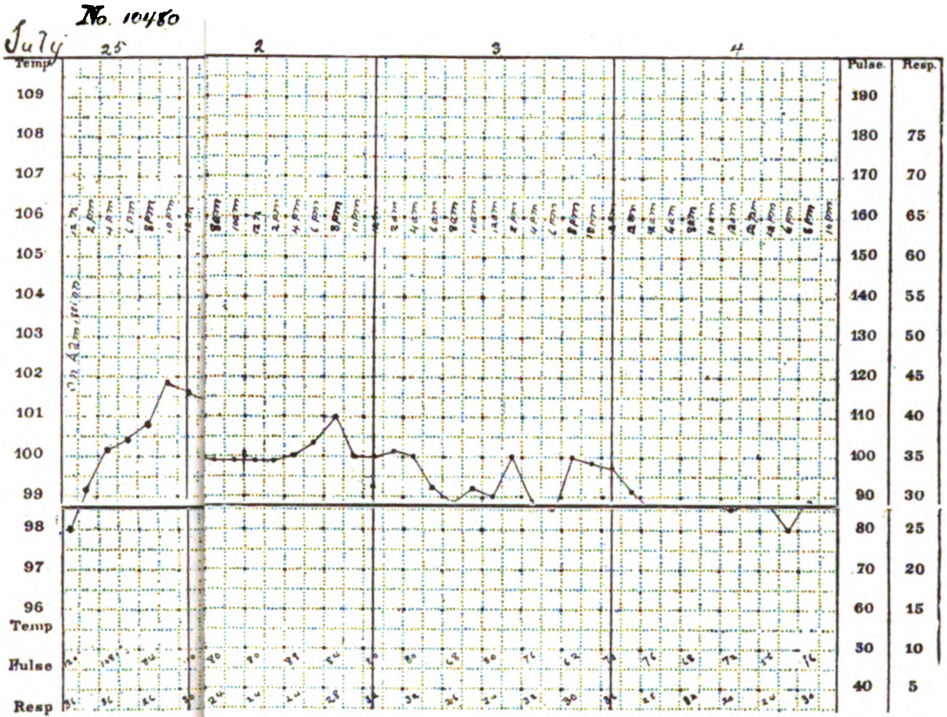
Blood at 9 a. m., negative; at 2 p. m., negative.

1–8–94. Temperature in the morning was 101.6°; at night, 102.6°. Whole left parotid gland greatly swollen, red and tender.

Blood. No organisms seen, excepting an occasional crescent. Leucocytes, 5000 to the cu. m. m. From this time on, no hyaline organisms were noted in the blood. The parotid swelling gradually disappeared, the temperature reaching normal on the 4th of August. The patient insisted on leaving the hospital on August 8th, when she felt perfectly well.

This case is of remarkable interest, in that it simulated typhoid fever so closely. The temperature showed a continuous elevation without intermissions; the tongue was dry and coated; the patient was, at first, in a drowsy typhoidal condition. The urine showed throughout a diazo reaction. There were no chills and no sweating while she was in the hospital. The presence of the amoeboid bodies in the blood alone revealed the true nature of the case. Moderate doses of quinine, begun on the 28th, showed, on the 30th and 31st, a slight influence upon the fever. No hyaline forms of the parasite were observed in the blood after the 31st. The appearance, however, of the parotitis on the evening of the 31st caused an elevation of temperature, which would lead one to believe, on superficial examination, that the process had not reacted to quinine.

This is one of those cases which shows the importance of the examination of the blood in all doubtful cases of fever. It is also of interest in that it was quite impossible to distinguish any separate groups of the parasites in the blood. No examples of the later stages of development were ever found. It is probable that here the spleen and internal organs contained multiple groups of organisms in all stages of development, while continuous segmentation and liberation of toxic substances was occurring throughout the course of the fever. The question may arise whether it is not possible that the case was one of typhoid fever combined with malarial fever. We see no reason to believe that this was the case. On entrance to the hospital, the patient's temperature was normal. She had had chills on at least one instance before entry. We are not justified in taking the patient's statements as indicative that the temperature before entry had been


No. 10480
July
25
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Temp
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Temp
Pulse
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Pulse.
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180
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Resp.
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5
On Admission

continuously elevated. It is not at all unlikely that it had been, at first, somewhat intermittent. As soon as the fall in temperature began, the patient was given a full diet, which was perfectly well borne. She was, also, able to be out of bed and about within two days after the time the temperature reached normal, without showing the debility which one would expect following typhoid fever. There were never, at any time, any abdominal symptoms.

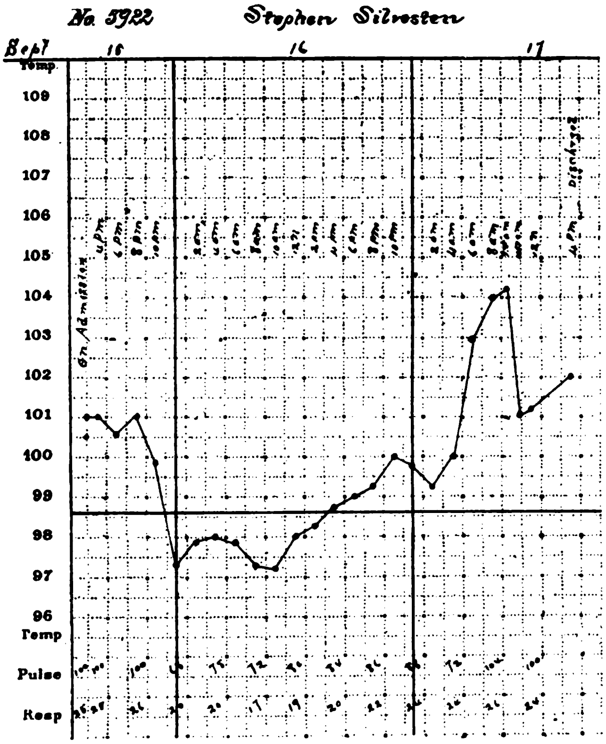
The following case is an interesting example of that class of cases in which the existence of malaria is often unsuspected, owing to the absence of any acute febrile symptoms.

CASE 7677.—The patient was a female, single, aged 23; mentally rather feeble; has never had malaria before. She was admitted on the 8th of July, 1893, complaining of an illness of six days' duration, of pain in the abdomen and vomiting; severe headache and general muscular pains; slight cough, anorexia; the vomitus was at times blood-stained; constipation; slight oedema of the feet and ankles. Physical examination showed a fairly well-nourished girl; tongue slightly coated; color good; thorax negative; abdomen negative; splenic border easily palpable. Patient was very nervous, and marked vaso-motor disturbances were seen on the skin. She was given, at first, a light, later a general diet; tincture of nux vomica. The urine was negative, barring a faint trace of albumen; no casts were found. An hasty examination of the *blood* showed no malarial organisms. The temperature, on entry, was 100°, but was never again above 99.5°, and, during the eight days that the patient was in the hospital, was, for the greater part of the time, sub-normal. The girl complained, however, bitterly and continually, of headache. On the 16th of July the patient, owing to a misunderstanding, was discharged.

She returned five days later, July 21st, complaining of the same symptoms. She was very dull and heavy; tongue thickly coated. Temperature 99.2° on entry; rose to 101.3° at twelve midnight, but was normal afterwards. Examination of the *blood*, on the 22nd, showed a few ovoid and crescentic pigmented parasites. On the 23rd there was a moderate number of pigmented crescentic and ovoid bodies, with an occasional hyaline, intra-cellular form, amoeboid or ring-shaped. On the 25th, the temperature still being normal, and the patient complaining bitterly of headache, she was given five grains of quinine every four hours. For several days after this the temperature was sub-normal. On the 27th no hyaline forms were to be seen, though numerous ovoids and crescents were present. On the 18th of August no malarial organisms were to be seen.

The following cases, 6 in number, are the only ones of surely tertian fever which we observed, though there are many in which this had existed, if we are to believe the statements of the patients.

CASE 5922.—S. S., single, aged 26, Pole, was admitted on the 15th of September, 1892. Patient could speak no English; he was a laborer, in a very malarious district. So far as could be made out, there had been no previous attack. Present illness began, two days before entry, with a shaking chill, accompanied by headache, fever and sweating. He had no chill yesterday, though he feels badly to-day. The patient was admitted with a temperature of 101°. By midnight it was sub-normal, and there was no fever till the evening of the 16th, when it began to rise gradually until, at 9.45 a. m. on the 17th, it had reached 104.2°. There was a fall after this time to 101.2° at noon. At 4 p. m., the temperature being 102°, the patient was discharged for insubordination. The *blood* on the 16th and 17th showed a few small, intra-cellular, hyaline bodies.



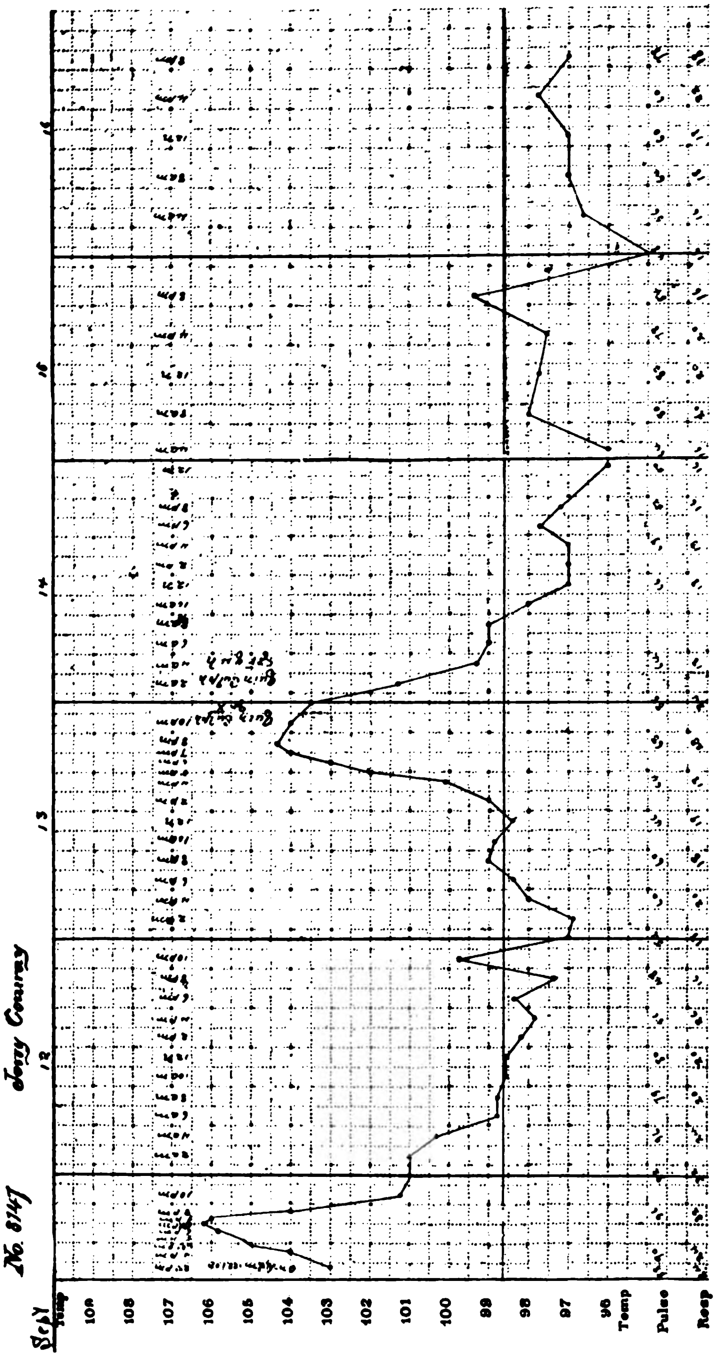
CASE 5923.—C. R., single, aged 25, Pole, admitted to the hospital on the 15th of September, 1892. He was a companion of the last patient, working with him in the same place. He has always been a healthy man; no serious illnesses previously. Present illness began two days before entry, when patient complained of chilly sensations, headache, fever and sweating. His symptoms came on at almost exactly the same time as those of his companion who lives in the same house and works at the same place. On entry the physical examination was negative, excepting for the palpable spleen. The urine contained a trace of albumen; no casts seen. As may

be seen by consulting the chart, the temperature, which was 101° at 8 p. m. on the 15th, was normal by 10 p. m., and remained so nearly all day, until the evening of the 16th, when it began again gradually to rise, reaching 102.4° at 6 a. m. on the 17th. It fell then to 100° at 8 a. m., rising gradually after this to 104° at 4 p. m., and reaching normal only between ten and twelve midnight, the paroxysm having lasted over thirty-eight hours. During the morning of the 18th, the temperature was normal, rising to 105.7° at 4 a. m., and falling to 102.8° at 8 a. m., with a second rise to 105° at noon on the 19th. There was another break in the fever between noon and 2 p. m., the temperature falling, in two hours, five degrees, and rising, gradually again, with chilly sensations, but without a shaking chill, to 103.8°, reaching normal by 2 a. m. on the 20th. Quinine, gr. ij (0.13) three times a day, was begun on the 17th. There was but a slight paroxysm on the 20th and the early morning of the 21st; a normal temperature afterwards. The examination of the *blood* showed, on the morning of the 16th, a very few small, intra-cellular, hyaline forms. At 8 a. m. on the 17th the same organisms were to be seen, still scanty. On the 18th and 19th the same forms were noted; at 8.30 a. m. on the 19th one form showed one or two fine pigment granules. The organisms disappeared rapidly under quinine, none being seen on the 21st and 23rd.

This case corresponds, well, to Marchiafava and Bignami's aestival-tertian fever, the paroxysm of the 16th and 17th showing, rather strikingly, the pseudo-crisis and the precritical elevation. The following paroxysm, however, was not so characteristic, showing several oscillations. The organisms, however, showed no apparent differences from those in the quotidian cases.

It is of considerable interest that these two cases of tertian fever should have occurred in companions, subjected to the same influences. The attacks began on the same day, and, in the hospital, the patients showed almost simultaneous paroxysms, both entering with fever on the 15th, the temperature reaching normal, in each case, between ten and twelve p. m., with a rise in temperature beginning, almost simultaneously, on the evening of the 16th in each instance.

CASE 8147.—J. C., colored, aged 39, laborer, admitted on September 11th, 1893; first attack. Illness began five days ago with pain in the back, headache, some abdominal pain, constipation; no chill, no nose bleed. Physical examination negative, excepting that the spleen was palpable. The patient entered during a paroxysm, the temperature at 2.45 p. m. having been 103°, reaching 106° at 6.30 p. m., and falling to normal by 6 a. m. The temperature remained normal during the 12th and the greater part of the 13th, starting to rise again between 3 and 4 p. m., and reaching 104.8° at 8 p. m., from which time it fell gradually, reaching the normal point at about 6 a. m. on the following morning. Quinine, gr. x (0.65), was given at the height of the paroxysm; gr. v (0.325) every four hours afterwards, the temperature remaining normal or sub-normal until discharge on the 20th. On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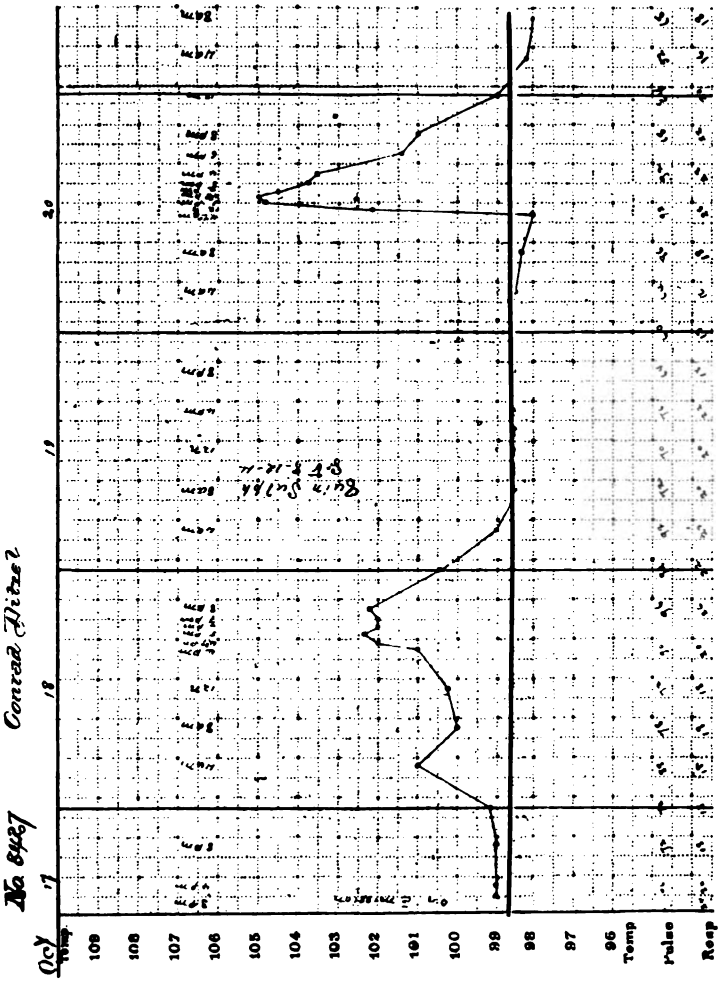
admission the *blood* showed a few small, hyaline malarial organisms. On the following day similar amoeboid, ring-like bodies were seen, but no pigmented forms were made out. During the 13th a few forms with occasional pigment granules were seen. On the 15th no malarial organisms were to be made out, and none were seen afterwards.

This would appear to be an undoubted example of a retarding tertian infection, though the temperature does not show the oscillations described by Marchiafava and Bignami as characteristic.



CASE 8427.—C. D., aged 54, stevedore; first attack; admitted October 17th, 1893. About a month ago had a shaking chill, followed by headache and fever, which continued through several days. Has had headache and fever most of the time since, with periodical sharp paroxysms, associated with shaking chills. On admission, the temperature was 99°. On the following day, shortly after midnight, there was a gradual rise in temperature, reaching 102.4° at 5 p. m., and reaching normal at about 4 a. m. on the 19th. Quinine, gr. v (0.325) every four hours, was ordered on the 19th, when the temperature was normal. On the morning of the 20th, between eleven and twelve o'clock, there was a sharp chill, the temperature reaching 105° at 1.30 p. m., and falling to 99° at about midnight. The patient left, early on the morning of the 21st, against advice. The *blood* on entry showed actively amoeboid, intra-cellular, hyaline bodies, several ovoid forms, one of which was filled with vacuoles of different sizes, apparently a degenerative form. At 8.30 p. m., two crescents and only one small hyaline, intra-cellular, ring-like form was seen. These small hyaline bodies, and crescentic forms, were seen throughout the patient's stay in the hospital; no segmenting forms, and no flagellate bodies were seen. It is interesting to note, that on the 20th, at 8.30 a. m., only one hyaline form was seen, after long search, while at 3 p. m., none were to be seen. Ovoid and crescentic forms were, however, noted.

Case 10465.—U. S. G., male, single, aged 25, laborer, admitted July 24th, 1894, complaining of headache, pain across the back, and chills. Has been ill for four days with headache and general pains; no chills; no nose bleed; some abdominal pain.

On entry, the temperature was 103.4°; rose to 105° at 4 p. m.; was normal at 6 a. m. on the following morning.

Blood, 2.30 p. m. A large number of amoeboid, hyaline, non-pigmented bodies; also smaller, more refractive, ring-like forms; two bodies with pigment collected in a central block; no actual segmenting forms.

8 p. m. Numerous amoeboid, hyaline organisms, ring-like forms, bodies with one or two grains of pigment, pigmented leucocytes. The course of the temperature is shown by the chart on the opposite page. It will be seen that the patient showed two paroxysms in the house; one beginning on the evening of the 25th, and one on the evening of the 27th, each showing the initial rise, the pseudo-crisis, and the precritical elevation described by Marchiafava and Bignami. The following are the notes of the blood and the urine, which may be compared with the temperature on the chart.

25–7–94. The urine showed a faint trace of albumen; no diazo reaction; no casts seen.

Blood, 8.45 a. m. Parasites appear a trifle larger than they were last night. There are not so many of the small ring-like forms, while a majority show an occasional pigment granule at the periphery. The amoeboid movements are less marked than they were last night. Several bodies contained in shrunken, crumpled, brassy corpuscles were seen; leucocytes containing pigment blocks.

2.30 p. m. Numerous ring-like hyaline bodies, many amoeboid forms, some pigmented.

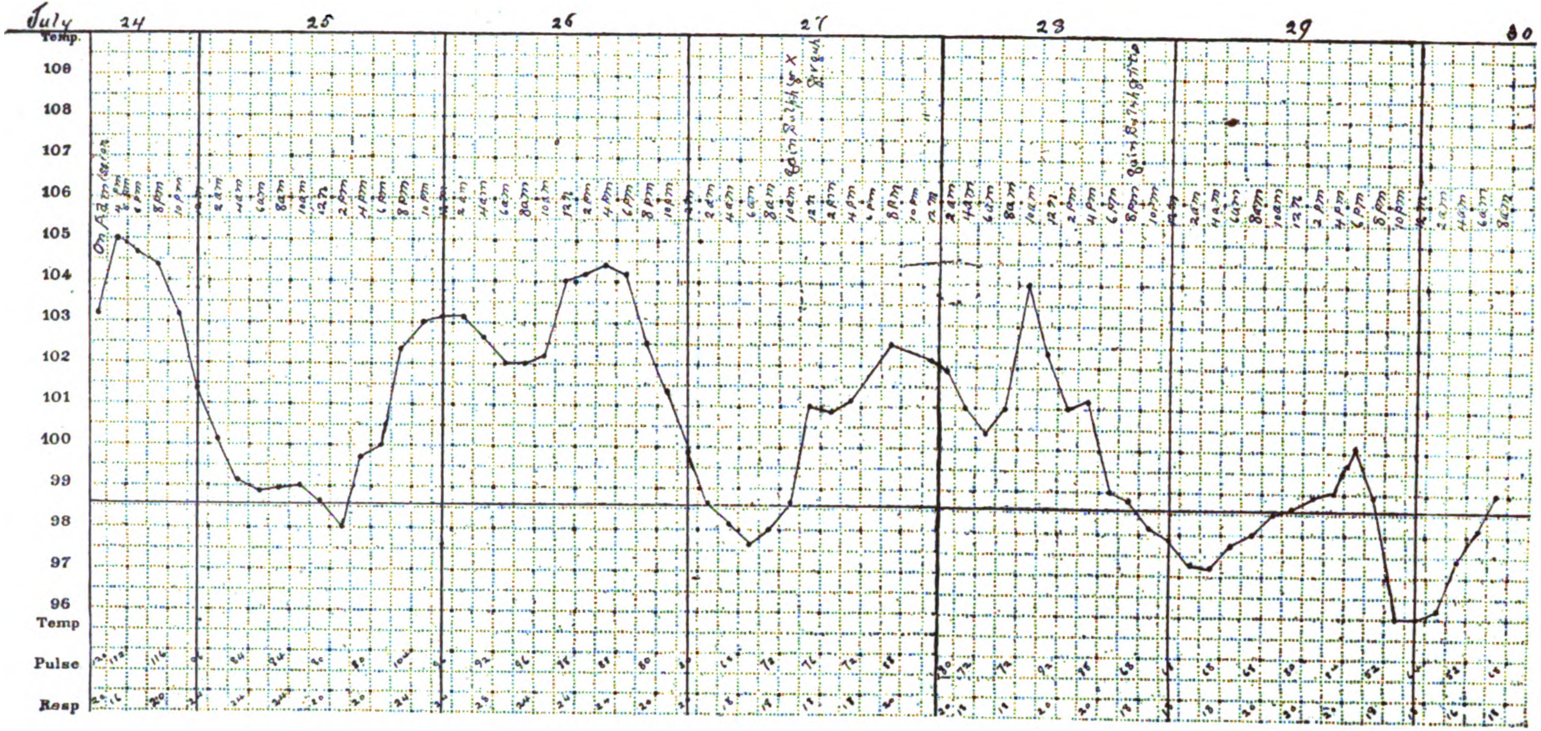
8 p. m. Temperature is beginning to rise. Examination of the blood showed nothing beyond one non-pigmented, ring-like form.

26–7–94. Blood, 9.30 a.m. Negative; no organisms seen.

2 p. m. A few ring-like bodies.

8 p. m. Numerous ring-like, amoeboid, hyaline bodies.

No. 10465 **U. S. Grant**



27–7–94. The blood shows a few actively amoeboid, hyaline bodies; a few ring-like forms; a few bodies showing occasional pigment granules.

2 p. m. Numerous larger ring-like forms, one showing two quite active pigment granules; one larger body with a clump of pigment in the middle; two leucocytes containing pigment blocks.

7.45 p. m. Blood showed a few hyaline, amoeboid, bodies. At noon, quinine, gr. x (0.65), were given, to be followed by gr. v (0.325) every four hours.

28–7–94. 8.30 a. m. Blood negative.

2 p. m. One crescent and one ovoid body, with coarse pigment granules in the middle; two pigmented leucocytes.

8 p. m. Crescentic bodies and numerous pigmented leucocytes.

29–7–94. Temperature normal. Blood at 10.15 a. m., negative. At 3 p. m., ovoid and crescentic bodies. At 8 p. m., the same.

30–7–94. Crescents still visible. There was a slight abortive rise in temperature on the evening of the 29th; temperature was normal on the 30th, when the patient insisted upon leaving the hospital.

This case shows, as far as the clinical chart goes, the closest approach to Marchiafava's and Bignami's aestival-tertian fever that we have seen. While the examination of the blood revealed, apparently, but one set of parasites, the few stages of development, however, which were visible, makes it impossible for us to say with certainty whether this was the case. There was, so far as we could discover, no difference between the morphological characters of these parasites and those associated with quotidian fever.

CASE 10534.—M. R., female, single, colored, aged 29; first attack. Duration? Entered the hospital July 31st, 1894, in an hysterical attack; opisthotonos, grinding of the teeth, tossing about, complaining of general soreness and pain, particularly in the left breast. Temperature, 100.1°; 101° at 8 p. m.; nearly normal the following morning; the blood not examined.

1–8–94. Patient is better, complaining only of headache; examination negative. Temperature, as noted on chart, beginning to rise during the evening.

2–8–94. Temperature elevated. Blood at 10 p. m. showed a considerable number of small, ring-shaped and amoeboid hyaline bodies.

3–8–94. Temperature normal during the morning, beginning to rise in the afternoon.

Blood, 3 p. m., showed a large number of hyaline bodies, many showing distinct spots of pigment, some smaller ring-shaped forms; pigmented leucocytes.

8 p. m. Numerous ring-like bodies, several hyaline forms with pigment granules; pigmented leucocytes.

4–8–94. Temperature elevated. Blood at 9 a. m. showed a few ring-like bodies with one or two hyaline forms; some pigmented leucocytes.

2 p. m. Several hyaline bodies; pigmented leucocytes.

7.30 p. m. A few ring-like bodies.

5–8–94. Quinine, gr. v (0.325), every four hours. Temperature normal.

9 a. m. A few ring-like bodies; one or two amoeboid forms.

3 p. m. A few ring-like bodies with one pigment granule; pigmented leucocytes.

7.20 p. m. A few ring-like bodies. Temperature beginning to rise.

6–8–94. Temperature normal. Blood negative at 9 a. m. and 2 p. m.

7, 8, 9, 10, 11–8–94. Temperature normal and blood negative.

14–8–94. Temperature normal. No blood examinations for several days. To-day, ovoid and crescentic forms are seen.

15–8–94. Ovoid, crescentic, round and flagellate bodies; pigmented leucocytes.

16–8–94. Crescents and ovoids; no flagellate bodies to-day at 2 and 8 p. m.

17–8–94. Crescents, ovoids, and flagellates; pigmented leucocytes, the pigment being in fine granules.

18–8–94. Blood examined at 9.30 a. m., 2 and 8 p. m.; only crescents and ovoids were seen.

19–8–94. Crescents, ovoids and flagellates.

20–8–94. Crescents and ovoids.

21–8–94. Crescents and ovoids.

From this time on the blood was negative. The chart here shows two anticipating tertian paroxysms; one of them shows the pseudo-crisis and pre-critical elevation described by Marchiafava and Bignami.

Examination of the blood, in this case, is particularly interesting, in that it shows the development of flagellate bodies ten days after the beginning of quinine, nine days after the temperature had been normal. These were found as late as the fourteenth day of normal temperature.

The following case is included as a possible instance of aestival-tertian fever, though the temperature was, for some time, continuous.

Case 7753.—J. W., married, aged 38, laborer, admitted 21st July, 1893. He says that he had intermittent fever at fifteen; has been, otherwise, always well. His present illness began four days before entry with a shaking chill in the morning, followed by fever and sweating. This was repeated two days ago, and to-day, July 21st, the patient entered the hospital with a temperature of 102.6°. The physical examination was negative; the spleen was not palpable. The urine showed a slight trace of albumen; no casts were found; a faint diazo reaction was present. The blood, on entry, showed only a few very small, ring-shaped, hyaline bodies. The chart shows the course of the fever.

On the 22nd, at 3.45 p. m., the blood showed but a few small, hyaline, ring-shaped bodies.

On the morning of the 23rd, at 9.45 a. m., the blood contained a very considerable number of hyaline organisms, some very small and often ring-shaped, others a trifle larger and amoeboid; no pigmented forms were seen. At 3.45 p. m. numerous hyaline bodies, slightly larger, but no pigmented forms. At 11 p. m. about the same appearance.

On the evening of the 24th the blood showed a similar appearance; still no pigmented forms.

On the 25th, at 10.30 a. m., the organisms were much more numerous than the night before, mostly a little larger than last night, and a few contained one or two very fine pigment granules.

On the 26th very few organisms; no pigmented forms. Quinine, gr. v (0.325), every four hours.

On the 27th, at 10.15 a. m., no pigmented forms seen. The organisms are less numerous.

28-7-93. Temperature normal; patient leaves at his own request.

In this case, a history of tertian paroxysms before entry was given, though the examination of the blood did not allow us to follow out the cycle of development of the organism. The temperature, however, is a good example of the more or less continuous variety of fever which is sometimes seen with this form of malaria. We have not included the case among those with tertian paroxysms, though we are inclined to think that Marchiafava and Bignami would place it under that heading. Does the continuous fever from the 22nd to the 24th and from the 24th to the 26th represent one or two paroxysms? The examination of the blood, not as complete as might have been wished, does not wholly clear up the matter.

The following case, though it is included, in our classification, among the combined infections, would, perhaps, be better mentioned among the aestival-tertian cases.

CASE 10529, male, single, aged 29, admitted July 31st, 1894, complaining of chills and fever; first attack. He has been feeling poorly for a month, having had chills and fever, he believes, at irregular intervals; general soreness, vomiting, variable appetite.

On entrance, temperature was 103.8°, reached 104.3° at 8 p. m., and was normal by early the following morning. The appended chart will show the course of the fever.

Blood, 6 p m., showed a few amoeboid, non-pigmented, hyaline bodies.

1-8-94. Physical examination showed a coated tongue, herpes on lips; spleen not palpable.

Blood. One amoeboid, hyaline body, with two spots of pigment, at 8.30 a. m.; at 9 a. m., the same; at 2 p. m., a few rather large ring-like bodies, more hyaline forms, several having distinct blocks of pigment.

8 p. m. Hyaline bodies a little larger, some ring-shaped, one nearly full-grown parasite, apparently of the tertian variety, the red corpuscle being expanded and decolorized, pigment granules in the body being brown, fine, and in active motion.

2-8-94. Blood, 9 a. m. Negative.

2 p. m. Numerous small ring-shaped bodies, few hyaline forms, several with distinct pigment granules, two larger bodies nearly filling the blood corpuscle, with a clump of pigment in the middle. Corpuscles were not expanded, but were rather pale.

8 p. m. Numerous small ring-shaped bodies, a considerable number of hyaline forms. The patient had two distinct chills, one at 2 a. m. and one at 2 p. m.

At 3 p. m. the patient was given quinine, gr. v (0.325), which was vomited. At 10 p. m., gr. x (0.65), afterwards gr. v (0.325), every four hours. During the afternoon, a most profuse urticarial eruption appeared over the whole body. About 7 p. m. patient suddenly sat up in bed; his eyes became fixed and staring, he fell back again muttering to himself, apparently quite unconscious; profuse sweating; face livid; pulse uncountable at the wrist; no biting of the tongue; no involuntary micturition or defecation; no rigidity of the limbs. In fifteen minutes the attack had passed off.

3–8–94. Temperature normal. Blood, 8.30 a. m., showed a fair number of amoeboid, hyaline bodies in unaltered corpuscles, some ring-like forms, occasional bodies with one or two minute pigment granules; pigmented leucocytes, the pigment being for the most part in fine granules.

3 p. m. A few ring-like hyaline bodies, several forms having minute pigment granules; pigmented leucocytes similar to those in the morning.

8 p. m. A few ring-like forms, two bodies having minute pigment granules.

4–8–94. The temperature rose early this morning with chill, another chill occurring at 4 p. m.

Blood, 9 a. m. A number of small hyaline bodies, one with a pigment granule, a few ring-like forms, one large, full-grown, swollen, extra-cellular tertian parasite, with pigment in active motion.

2.45 p. m. One body filling about two-thirds of the red corpuscle, containing a central clump of pigment in active motion; several pigmented leucocytes.

5–8–94. Temperature normal. Examination of the blood at 9 a. m., 3 and 7.20 p. m., showed a few ring-like bodies and pigmented leucocytes.

The blood of the 6th and 7th of August showed no organisms.

8–8–94. One pigmented leucocyte with scattered granules.

8–9–94. No organisms seen; patient discharged.

This case is interesting from several standpoints. As with all the other cases of combined infection which have been noted, while organisms of both tertian and aestivo-autumnal types were present, one of these types—in this case the aestivo-autumnal—was preponderant, causing all the symptoms. It is an interesting question as to how we should regard the chart. Was the elevated temperature between the early morning of the 2nd and the morning of the 3rd a single paroxysm, and the case one with intervals of about fifty-two hours, or are we to assume that we were dealing with multiple groups of parasites? We do not feel that the examination of the blood justifies a conclusion. It is an interesting point, that on the 2nd there were two chills, one at 2 a. m., and another at 2 p. m.; while on the 4th there were also two chills, one at 6 a. m., and one at 4 p. m. The marked irregularity of the temperature between the 2nd and 3rd is striking. It may, also, be noted that there was a slight rise of temperature at noon on the 1st. The presence of occasional presegmenting forms during the paroxysms is of interest. The curious nervous manifestations, during the paroxysm on the second, may have been dependent upon some interference with the intra-cerebral circulation on the part of the parasites.

CASES OF PERNICIOUS MALARIAL FEVER.

Only three cases of pernicious fever have been admitted to the hospital since its opening. Of these, two resulted fatally, and one recovered. The first two cases we will quote from Dr. Osler's note in the Johns Hopkins Hospital Bulletin, December, 1891.

CASE 131.—Lewis K., admitted July 18, 1889, complaining of pains in the head and of coldness and numbness of the feet and hands. He has enjoyed fairly good health, and, for his age, is a vigorous, healthy-looking man. On the 9th, while picking berries in a field in Anne Arundel county, he had a heat stroke; was unconscious for two hours, and had to be carried home. He was up the next day and was able to work; has not felt well since, and has had headache and occasional feelings of sensation of cold.

On the 18th the following note was made: Healthy-looking, much sun-burnt, pulse full, vessel-walls soft, no oedema of feet. The lungs are clear in front and behind; respiration is a little prolonged. The apex beat of heart is neither visible nor palpable; the sounds are weak, the second is scarcely audible at base. The area of liver dullness is reduced; the spleen not enlarged. The urine is light yellow in color, specific gravity 1010; no albumen or casts.

I saw the patient only during the first four days of his stay at the hospital, and thought that he was suffering from the effects of a sun-stroke. He was given a tonic mixture. The patient's temperature was normal, but on the 20th and 21st the morning record was 97.6° and 97.8°.

On the 25th, at 11.30, he had a chill, and the temperature rose to 105° and remained high all afternoon. At 7.30 p. m. it was again 105°, and he had a graduated bath.

Throughout the 26th the temperature fell, but did not get below 101°; the pulse was rapid and feeble.

On the 27th the temperature at 8 a. m. was 100.5°; rose in the afternoon to 103°, and in the evening was 100.3°; pulse 104, extremely irregular and intermittent. There were feeble râles, with a high-pitched percussion note in right infra-scapular region. Towards evening the patient sweated profusely, and the breathing was of the Cheyne-Stokes type.

On the 28th the temperature fell rapidly, sinking from 103° at 4 p. m. of the 27th to 97.3° at 8 a. m. of the 28th, and to 95.5° at 10 a. m. The pulse is extremely feeble and irregular. He vomited twice; no expectoration. There was marked feebleness of breathing at the right base. Throughout the afternoon of the 28th the temperature rose, and at 8 p. m. was 100°.

29th. Cheyne-Stokes respiration persists; has had slight diarrhoea. He speaks with difficulty, but appears to be conscious.

Throughout the 30th and August 1st he gradually sank, and died on the morning of the 2d.

I did not see this patient from the date of his chill until the morning of the 2d, just before his death. The case was regarded as one of low anomalous pneumonia. The day after the chill it is stated in the note that the blood was examined with negative results; but there is no initial to indicate by whom the examination was made.

The following note of the microscopic examination was appended to the post-mortem report by Dr. Welch: "Blood from the finger shows in small numbers malarial organisms, namely, spots of the shape and size of the red blood corpuscles with pigmented plasmodia, free round pigmented corpuscles, varying in size from blood plates to twice that size, and pigmented crescents, the pigments in a ring in the middle. I found in one specimen of splenic pulp two actively free flagella. In the capillaries of the brain are a few pigmented corpuscles."

CASE 1769.—J. B., aged 34, admitted September 10th, 1890. I saw him in the dispensary at 1.30 p. m. He was very weak and tremulous, with eyes congested and cheeks flushed, and with a dazed, stupid appearance. The tongue was swollen, heavily furred and indented. He looked like a man who had been drinking, and I told his brother that it would be impossible for us to admit him to the wards in his present state. He assured me, however, that he had not been drinking to excess, and on ascertaining that there was not the slightest trace of alcoholic odor in the breath, I signed the order for his admission.

The following history was obtained. Family and personal history good. The patient is a sailor by occupation, and has enjoyed excellent health; he left Boston for Savannah five weeks ago; spent a week in the latter place, and as the weather was oppressive he, with several of his shipmates, was in the habit of sleeping upon the grass all night. He remained well on the voyage to Baltimore, where he landed August 31st. He was about the house all week, not feeling quite himself, but the present illness dates from Sunday the 7th, when, without any chill or fever, he began to have vomiting. He felt extremely weak and prostrated, so that he could not get up on Monday morning. Throughout Monday and Tuesday the vomiting continued at intervals, and he was completely prostrated. He had no chills, but on Monday and Tuesday he took some quinine pills. In the dispensary, after failing to detect any alcoholic odor in his breath, and on learning that he had recently come from the South, the blood was at once examined; large numbers of Laveran's organisms were found, which rendered the diagnosis clear. His temperature on admission in the ward was 101°; pulse 104, small; tension not increased; radials not stiff. The abdomen was soft; nowhere tender. The edge of spleen was just palpable on deep inspiration; upper border of dulness at the ninth rib.

Apex beat of heart in 5th interspace within nipple line; sounds clear; examination of the lungs negative.

Blood. Small intra-corpuscular forms in extraordinary abundance, often 6 or 8, to be seen in the field of the $\frac{1}{12}$ im. The majority of them are not pigmented, and undergo very rapid changes in outline. The pigmented forms have the granules more concentrated than is usual in this stage of the evolution of the parasites. An unusual number of the leucocytes presented pigment granules.

11th. Very bad night; much vomiting; temperature sank to 98.6° at 10 a. m., and to 98.2° by 8 a. m. At the morning visit the patient looked depressed; tongue heavily furred; pulse 80, small and thready; respirations 20. Has no headache, and complains chiefly of profound weakness. At noon the temperature began to rise, and at 4 p. m. reached 102.2°, and for six or eight hours remained about 102°, gradually falling through the early morning hours, and at 8 a. m. reaching 98.5°. The blood condition remains practically the same.

12th. 10 a. m. Patient passed a better night. The vomiting has stopped, but the tongue is still furred; no increase in splenic dulness. The bowels have been freely opened. He still looks depressed and dull, and complains of a feeling of great prostration.

13th. Temperature has been about 98° for the past twenty-four hours, pulse 72, small. The vomiting has not been so distressing, and he has taken the milk and brandy better than on any day since admission. The blood examination shows a marked diminution in the number of corpuscles containing the plasmodia, doubtless under the influence of the quinine.

14th. Temperature has been sub-normal, not rising above 97.5° all day. The vomiting has returned, and for the first time it contained blood, not in large amount, but sufficient to color the fluid. His mind is perfectly clear, and his sole complaint is of the extreme depression.

15th. 10 a. m. Patient's condition is worse since 8 p. m. last evening. The temperature has been below 97°, and at 12 midnight sank to 96°; pulse 64, respirations 20. Tongue still swollen, heavily furred and indented. Note on the blood to-day is: "Plasmodia very much diminished in number; leucocytes still show much pigmentation." The urine is amber colored, specific gravity 1010, acid and contained a slight amount of albumen. At 9 p. m. I made the following note: patient is in a very peculiar condition; is drowsy, dull, roused with difficulty, and does not answer clearly. He has behaved oddly all day, and has been very restless. There has been very little vomiting; temperature has been sub-normal, and is now 96.5°. For the first time the tongue is distinctly dry.

16th. Through the night the patient was very restless, and had much hiccough; was not delirious, but acted queerly. The temperature sank through the night, and at 2 a. m. was 96°; at 4 a. m. the thermometer could not be made to register more than 95°, and remained at this point until 10 a. m. The vomited matter last night contained flakes of blood enough to tinge the whole fluid. He had retention of urine, and this morning 1500 cc. were withdrawn, which showed a narrow ring of albumen and contained hyaline and granular tube-casts. The nurse says that he does not understand questions, but he seemed to recognize me, and gave fairly rational answers, but complained of great oppression in the abdomen. The pulse is 72, and, considering his condition, the volume and tension were remarkably good. At 6 p. m. I made the following note: temperature has risen through the day, and is now 97.2°. The tongue is dry, pulse 96, regular and of very fair volume. He is extremely restless, and his face has a dusky hue; the respirations are at times gasping, 24 to the minute. He answers questions, but talks and rambles in an incoherent way. To-day very few red blood corpuscles containing plasmodia have been found; the leucocytes are still much pigmented. Patient became much more restless, threw himself about on the bed, then became unconscious, and died at 8 o'clock. The treatment consisted of half drachm doses of quinine every six hours, which was given hypodermically when the vomiting became excessive.

The drawings made from the blood in this case showed most characteristic aestivo-autumnal parasites.

A further comment upon the anatomical lesions in these cases will be found, in another part of this fasciculus, in the article by Dr. Barker.

The first of these cases is a very interesting example of death with a sub-normal temperature, occurring after the number of malarial parasites had been materially reduced by quinine.

CASE 10419.—F. O., single, aged 40, commercial traveller, admitted to the hospital July 19th, 1894. The patient, on entrance, could give no history, but from friends, and, later on, from himself, the following notes were obtained:

Since the 11th of June the patient has been travelling for the greater part of the ime in very malarious districts further south, having been "on the road" all the way from Maryland to Florida. For three weeks before entrance patient had not felt well, having, he believes, had fever off and on, but never chills nor sweating. His appetite was poor; he had considerable headache and, at times, nausea. He took to bed on the 16th, and became dull and stupid, recognizing no one after the morning of the 18th; no diarrhoea; troubled much with hiccough for six days before admission.

Immediately after admission the patient was seen and the following note was made: "Large, well-formed man, rather corpulent; is lying on his back in bed; respirations quiet, ten to the quarter; pulse regular and full, twenty-seven to the quarter, rather soft. The patient is quite comatose; the eyes are closed, the mouth open. A clonic spasm of the lower facial muscles on the left side is frequently noted, the mouth being drawn a trifle to the left. Pupils are equal, of moderate size, react readily to light on raising the lids. There is a well-marked sub-icteroid tint to the skin and to the conjunctivae, and the urine, which has been passed involuntarily, stains the bed clothing a markedly yellow color.

Thorax; negative on auscultation and percussion.

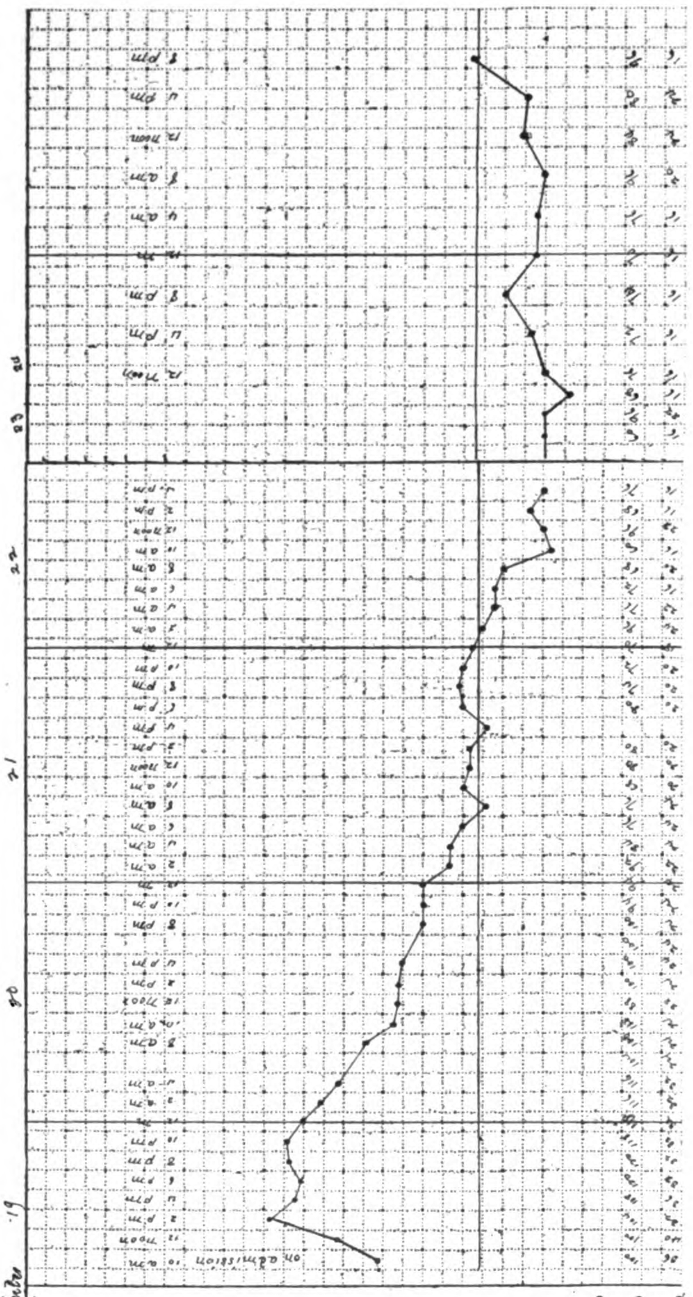
Heart; point of maximum impulse in the fifth space a little inside the mammillary line; relative dulness at the fourth rib; does not pass left sternal margin; sounds clear, of normal relative intensity.

Hepatic flatness begins at the fifth space, and reaches about to the costal margin; the border is not palpable, possibly because of the lack of deep respirations.

Splenic flatness begins at the eighth space and reaches anteriorly to the costal margin. The border is not distinctly palpable. The extremities are relaxed; there is no increase of the reflexes. While the patient does not answer questions, and pays no attention to sharp requests to put out the tongue, he occasionally moves an extremity, and when one grasps his hand, he makes a slight effort to close his fingers."

Examination of the *blood* at the bedside showed a considerable number of the smallest ring-shaped, intra-cellular, hyaline bodies, situated, for the most part, in

No. M. F. O


July
19
20
21
22
23
24
on admission
Temp
109
108
107
106
105
104
103
102
101
100
99
98
97
96
Temp
Pulse
Resp

crumpled, brassy-colored corpuscles. In one of these the haemoglobin was noted to have retracted from the outline of the corpuscle about the ring-shaped organism. No apparent leucocytosis; no pigmented parasites nor pigmented leucocytes. Muriate of quinine and urea, gr. xx (1.3), was immediately given hypodermically. Surprised by the hypodermic injection, the patient started for a moment, opened his eyes, and turned over in bed. Afterwards he had a slight attack of hiccough, lasting not more than a minute. The *urine*, on admission, was of a mahogany brown color, bile-stained, clear, acid, 1021, faint trace of albumen, no diazo reaction, no sugar, microscopically, negative. Temperature rose to 103.8° at 2 p. m.

Blood. 11 a. m. A considerable number of small ring-shaped and amoeboid hyaline bodies. Almost the majority of these were contained in crumpled, brassy-colored corpuscles. In many the haemoglobin was retracted about the organisms.

At 12 m.; the same appearance, excepting that in one parasite a few minute pigment granules were seen.

At 2.15 p. m.; organisms much more scanty, almost all ring-shaped, in crumpled corpuscles.

From 3 to 5 p. m., various examinations showed similar appearances.

At 8.30 p. m.; organisms very scanty, mostly ring-shaped and amoeboid hyaline bodies. One was seen about one-quarter the diameter of a red corpuscle, with several pigment granules in the middle. It was lying in a crumpled, brassy colored, corpuscle with retracted protoplasm. During the afternoon the patient became more restless and a little brighter, tossing about much in the bed. He opened his eyes when spoken to, and occasionally answered a question, but was confused and wandering. Muriate of quinine and urea, ten grains, (0.65), hypodermically, at 5 p. m. and 11 p. m.

20–7–94. Temperature 101.4° at 8 a. m. This morning, is tossing about in bed and restless, occasionally mumbling to himself. He answers sharp questions in a confused manner. Patient was fed yesterday entirely by enemata; to-day takes liquids. ℞. Sulphate of quinine, gr. v (0.32), every four hours. Temperature, by evening, had fallen to 100°.

The blood, in the morning, showed a number of intra-cellular hyaline forms, amoeboid and ring-like; no pigmented forms; no crescents. Late in the afternoon, but a few hyaline bodies were seen in two specimens.

21–7–94. The following note was made: "The temperature, which on entry was 101.2°, rose, on the afternoon of the 19th, to 103.4°, since when it has steadily fallen, until 8 a. m. to-day, when it is 98.3°. Throughout the day yesterday the patient became gradually clearer mentally, and to-day is quite rational. Ever since the afternoon of the 19th the patient has had obstinate hiccough for the greater part of the time. The slight jaundice still persists; pulse and respiration are slow and quiet. The spleen is readily palpable on inspiration. He is taking quinine, gr. v (0.325), every four hours. The blood shows only an occasional intra-cellular hyaline body."

22–7–94. Temperature normal. The speech, which has been a little thick before this, is quite clear. The blood showed but one hyaline body after long search. The urine is normal in color, free from bile, no albumen.

23–7–94. No hiccough since yesterday. From this time onward recovery was steady; no further organisms were found in the blood.

30–7–94. Leaves to-day, well.

This case is one of considerable interest in as much as it is the only example of comatose pernicious fever which we have had in the hospital. A particularly interesting point is the fact that, notwithstanding the severity of the symptoms, but few organisms, and those almost entirely the very small hyaline forms, were found in the peripheral circulation. The hiccough and the spasm of the lower facial muscles on the left side, as well, also, as the slight thickness in enunciation, are interesting points.

It will be noted that all these cases showed the aestivo-autumnal organisms, and, while severe symptoms may occur during the paroxysms in cases of tertian fever (delirium, etc.), true pernicious fever we have only observed in aestivo-autumnal infection, an observation which agrees entirely with those of the Italian and Russian authors who have dealt particularly with such cases.

The analysis of the types of fever in these cases certainly justifies us in distinguishing, sharply, the fevers associated with the aestivo-autumnal organisms, from those seen in the ordinary tertian or quartan infections. While, as has been previously noted, certain cases show charts not unlike those of tertian or quartan infections, the majority show distinctly longer paroxysms, lasting, on an average, at least nineteen or twenty hours, and frequently overlapping one another, causing continuous fever. The proportion of continuous and irregular fevers is much greater than in tertian infections. The individual paroxysms differ further from those in tertian or quartan fever, in that, in many, the rise of temperature is more gradual, frequently occurring without the sharp initial rigor.* Acknowledging, then, these differences between the regularly intermittent and the aestivo-autumnal fevers, can we distinguish any ground type or types among the latter? We have learned to recognize, in the regularly intermittent fevers (tertian and quartan infections), that the febrile symptoms bear a distinct, direct relation to the life history of the specific parasite; that the paroxysm is always associated with the arrival of a group of organisms at maturity and with their segmentation. The observations of numerous students, particularly in Italy, make it probable that this paroxysm is due to toxic substances set free

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* The term initial rigor, however, it should be remembered, is not always correct, as neither in tertian nor in aestivo-autumnal fever, can the chill be regarded with certainty as the initial step in the paroxysm.

by the parasites at the time of their segmentation. Do these rules, which apply so accurately to the regularly intermittent, tertian and quartan fevers, hold also for the aestivo-autumnal infections. If they do, how are we to account for the great variation in the febrile manifestations?

The cycle of development of the tertian and quartan organisms is easily followed out by the examination of the blood taken from peripheral vessels. We find the organism, in all stages of its development, in blood from the capillaries of the finger or the ear, and it has been shown, in a most interesting manner, that, just as in certain tertian and quartan fevers the paroxysms anticipate one another slightly, or show a tendency toward retardation, so the parasites, particularly of tertian fever, may, in certain instances, show a tendency to earlier segmentation, bodies being found in the process of sporulation which have not yet reached the ordinary full development, showing a smaller number of segments than is usually seen. In other words, it has been shown that while, regularly, the cycle of development of the tertian organism lasts approximately forty-eight hours, we may, not infrequently, see a parasite which matures every forty-six hours, or indeed, in some instances, every forty-four hours, or perhaps, in forty hours, while in others the cycle may take a somewhat longer time than the ordinary two days. And in all these instances the febrile manifestations follow the same course as the parasite, anticipating or retarding as the case may be.

Now are we to explain the irregularity of the aestivo-autumnal fevers by assuming a variability in the length of time required for the development of the parasite, recognizing, also, the frequency of infections with multiple groups of organisms? Must we assume that one of the chief characteristics of these infections is the extreme variability in the length of the cycle of development of the parasites, a variability dependent, perhaps, upon the malignity of the organism or upon the resistance of the individual affected; in other words, that this type of fever is essentially irregular? Or must we assume that there are two or more ground types of aestivo-autumnal fever dependent upon two or more varieties of the parasite?

From the observations which we have made, we feel that it is probable that there are aestivo-autumnal infections with but one group of organisms, which show daily paroxysms. Likewise, it appears to be true that there are other fevers which, with one group of organisms, show paroxysms occurring at intervals of forty-eight hours or even more. It may also be stated that in most of the cases with longer intervals the paroxysms have been rather unusually long, while, in some instances, paroxysms strongly resembling those described by Marchiafava and Bignami as dependent upon their aestival-tertian organisms, have been seen. In some of these, however, as in Case 7753, it is most difficult to say whether we are really dealing, in each instance, with a single or with multiple paroxysms, while, owing to the few stages of development of the parasite which are found in the peripheral circulation, and to the small number of parasites which we see altogether in some cases, we do not receive the same assistance from examination of the blood that is given to us in the tertian and quartan fevers. Moreover, in these cases with quotidian and tertian chills, we do not see the same regularity in the hour of development of the paroxysms that we note in tertian and quartan infections; the variations are so great that it is not at all clear that we can draw a distinction between the two forms. Do we not rather see every intermediate stage between the two? We have certainly been unable to make any sharp distinction between the cases with tertian paroxysms, and other cases where the paroxysms occurred, instead of, perhaps, at intervals of forty-eight hours, rather at intervals of between twenty-four and forty-eight hours, suggesting, thus, a connecting link between the two forms of fever. Had we been able to distinguish, in these cases, any marked differences between the organisms observed in each, such as exists between the organisms of tertian and quartan fever, we might have been led to suspect that there were, in reality, two distinct types of infection. But this is not the case. As a matter of fact, the organisms, in our few cases with tertian paroxysms, have had all the characteristics of those observed in the other forms of aestivo-autumnal infection. We have not, unfortunately, been able to study carefully the later stages of development of the segmenting bodies, but the differences pointed out by Marchiafava and Bignami in the development of the organisms and in their segmentation, appear to us too slight to justify the division that they have made. These differences appear to us to be scarcely greater than those between the ordinary tertian parasite and the tertian parasite which assumes a slightly more hasty development, and undergoes precocious segmentation. The differences consist almost entirely in the size of the adult forms, in the quantity of pigment which is present, and in the number of segments found, the organism which has taken longer to develop growing slightly larger, showing slightly more pigment, and a greater number of segments.

In conclusion, then, we have been able to distinguish, in infections with the aestivo-autumnal parasite, fevers with paroxysms occurring at intervals of about twenty-four hours, as well as others with intervals of about forty-eight hours, more or less. But we find, also, intermediate forms which constitute a connecting link between these two varieties of fever. The fevers with longer intervals show, generally, longer paroxysms. There is a large class of cases showing a more or less continuous fever where it is impossible to distinguish any ground type. We have been unable to distinguish any morphological or biological differences between the parasites associated with these various types of fever. In most cases, owing to the fact that but the earliest stages of development of the parasites are to be found in the peripheral circulation, and, sometimes, owing to the very small number of parasites which is to be found altogether, we are quite unable to distinguish whether we are dealing with one or with more groups of parasites. In a few cases, however, with characteristically intermittent fever, the examination of the blood, taken in connection with the course of the fever, has suggested to us that we were dealing with single groups of parasites whose cycle of development lasted from twenty-four hours or less, to forty-eight hours or a little more. The fever in these instances, as in the case of the tertian and quartan intermittents, we believe to be due to some toxic substance set free at the time of sporulation; it is essentially intermittent, and it is undoubtedly the fact that this intermittency is more evident in those cases which are observed at the beginning of their course. Though our studies of the parasite have been made almost entirely in the circulating blood, and do not justify a positive conclusion, we are, however, inclined to believe that the irregularity in the febrile manifestations is due chiefly; to the tendency on the part of the parasite to irregularities in the length of its cycle of development; to the fact that the period of time required for the sporulation of one group of organisms is materially greater than in the regular infections, owing to the fact that the arrangement of the parasites in definite sharp groups, sporulating nearly at the same time, is much less distinct than in the tertian and quartan intermittents; to the fact that, frequently, organisms in all stages of development are present at one time, segmentation occurring almost continuously.

We do not believe, then, that we can, as yet, separate the aestivo-autumnal fevers into two or more distinct types.

With regard to the relations of the crescentic and ovoid bodies to the febrile manifestations, we shall speak later on. We are not, as yet, inclined to accept the view of Bignami, Marchiafava, et al., that they are degenerative forms, though we have never been able to trace their sporulation.

Much, however, remains to be done in the study and analysis of these fevers; a systematic study of the splenic as well as the peripheral blood should be carried out.

COMBINED INFECTIONS.

The cases of combined aestivo-autumnal and tertian infection observed were eleven in number. Of these nine were seen in the hospital, and two in the dispensary.

CASE 1.—The first case was that of a man, single, aged 17, admitted to the hospital October 27th. Family history good; no previous illnesses. This is the first attack of malarial fever. Illness began fourteen days ago with chill, followed by fever and sweating. This has been repeated every day, chills occurring at about ten in the morning. The physical examination was negative, excepting for the palpable spleen; urine, negative. The *blood* showed numerous large, amoeboid, pigmented, intra-cellular organisms, characteristic of tertian fever, and the case was considered one of double tertian infection. The chart showed characteristic quotidian paroxysms with periods of subnormal temperature. The patient was treated with methylene blue, 0.1 five times a day, beginning on October 29th. After November 3rd the temperature was nearly normal, rising, however, slightly above 99° every day. The tertian organisms disappeared rapidly from the blood, but on November 3rd, five days after entrance, nineteen days after the beginning of the paroxysms, the patient showed crescentic and ovoid bodies characteristic of aestivo-autumnal malaria. On November 7th a few actively motile, small, hyaline bodies were also to be seen. Four days later the patient was discharged, the blood showing at this time no organisms. Eleven days later the patient returned to the dispensary, complaining of headache, loss of appetite, and thirst. The blood showed again crescentic and hyaline bodies, no tertian organisms. The patient was given quinine and was lost sight of.

CASE 2 (4847).—A little girl, aged 7, admitted to the hospital on the 10th of March, 1892. For five or six months before entrance the child had suffered from quotidian paroxysms. She had had treatment, off and on, ever since then, the chills being at times tertian, and again irregular, according to the history. At other times she complained only of continued fever, headache, and sweating. On entering the hospital, tertian organisms were found in the *blood*, one strong group, and one group less developed. The temperature chart showed typical paroxysms on the 12th and 14th of March, the temperature being slightly elevated on the days between, but showing no sharp paroxysms. On the 14th, beside the typical tertian organisms, one crescent was seen. Quinine was given eight days after entrance, the paroxysms having disappeared on the sixth. The tertian organisms disappeared quite rapidly, but crescents were found in the blood for some time afterwards, while small, hyaline, actively amoeboid bodies, in association with the crescents, were noted for some time after the tertian forms had ceased to appear. The last date on which organisms were seen was on the 22nd of March, three days after the beginning of quinine. On this date a small, ring-like hyaline body was noted.

This case is interesting in that it showed a spontaneous disappearance of the tertian infection after rest in bed and tonic treatment, while the small organisms characteristic of aestivo-autumnal fever, being more resistant, continued present in the blood, only to disappear after the beginning of quinine.

CASE 3 (5387).—A colored man, aged 32, admitted to the hospital June 15th, 1892. He had had his first attack of malarial fever during the fall before, no chills having occurred since January. Six days before entrance he had a shaking chill, lasting two hours, followed by fever, headache, and sweating; another, two days after this, and a third, two days later, the last occurring the day before entrance. The patient was a well formed man. Physical examination; negative, excepting for the palpable spleen. On the day of entrance the patient had a typical tertian paroxysm, lasting twelve hours, the temperature remaining below 99.8°, after this, without the administration of quinine. The *blood* showed, in the hospital, at the time of the chill, typical tertian organisms. Numerous segmenting bodies were seen, all showing from twelve to twenty segments. One of these bodies was of unusually small size, not having entirely filled the corpuscle. One typical crescentic body was seen. The tertian organisms disappeared entirely during rest in bed, and, after the 13th, only ovoid and crescentic forms were found. The patient was discharged on the 15th with a prescription for two grains (0.13) of quinine three times a day.

In this instance the symptoms appeared to be entirely due to the tertian organisms. It was probably a case of fresh tertian infection engrafted upon an old, attenuated aestivo-autumnal infection dating from the previous fall.

CASE 4 (6090).—Male, aged 20, Pole, first attack of malaria, admitted to the hospital October 9th, 1892. He dates his illness back five weeks before entrance, having had, at first, daily paroxysms, which had continued, off and on, up to the time of entry. The patient was anaemic, but otherwise the physical examination was negative, barring the palpable spleen. He showed a well-marked paroxysm on the day of entrance, and a slight rise on the following day. Quinine was given immediately, and the temperature was normal afterwards. The blood showed, at first, typical tertian organisms. On the second day after entrance crescents were found. On the 15th no organisms were to be seen. He remained in the hospital, taking quinine, until the fifteenth day of the next month, and was discharged well.

This case occurred at the season of the year when aestivo-autumnal malaria is particularly common; the patient had had paroxysms off and on for a number of weeks before entrance. It was doubtless a case of double infection.

CASE 5 (6748).—A man, aged 23, admitted February 9th, 1893. He had arrived, a month before entrance, from Cuba, where he had had various malarial attacks. He showed, on entrance, a typical double tertian infection. The paroxysms disappeared immediately after the administration of quinine on the 11th, and no organisms were seen on the 15th. Nearly a month later, while in the surgical ward, where the patient had been operated upon for hernia, typical crescentic bodies were found in the blood. On April 4th, the patient returned, complaining of headache, anorexia and slight fever. The blood showed a typical aestivo-autumnal infection; hyaline bodies, ovoid and crescentic forms.

Doubtless the crescents, here, were the remnants of an old aestivo-autumnal infection. The tertian infection yielded readily to quinine, while the more resistant aestivo-autumnal parasites remained, causing a relapse.

CASE 6 (8302).—A young man, aged 30, admitted to the hospital October 2d, 1893; first attack. Two weeks ago, after working on the Shell road for about a week, he complained of headache and general lassitude, slight chill and vomiting. Since then he has had nearly daily chills, with headache, fever and sweating. In the hospital the patient had a paroxysm on entry and one on each of the following days, lasting respectively 19 and 10 hours. The blood showed great numbers of aestivo-autumnal organisms, small, hyaline, amoeboid bodies, some showing occasional minute pigment granules, and also a certain number of tertian forms. Ten days later crescents were seen. Quinine was begun on entry, the tertian organisms disappearing rapidly, and the temperature remaining normal after two days.

In this case, also, there were clearly two distinct sets of organisms; the paroxysms here were apparently due to the aestivo-autumnal rather than to the tertian infection.

CASE 7 (8317).—Female, married, aged 27, admitted to the hospital October 4th, 1893; first attack. Present illness began about a month before entry with a shaking chill, followed by fever and sweating, which was relieved by quinine. For four days the legs have been swollen. The patient was in the seventh month of pregnancy. The temperature was never above 99.5°; the spleen was readily palpable. There was well-marked aortic insufficiency. The *blood* contained numerous ring-shaped and amoeboid hyaline bodies, and crescents; one tertian organism was also seen. Quinine was given on the day of entrance, and, after three days, no organisms were seen. The patient had been living in a very malarious district, and had undoubtedly suffered from a combined infection.

CASE 8 (8454).—Man, aged 23, admitted October 25th, 1893; first attack. He had been living in an extremely malarious district. His complaint, on entrance, was of general weakness and chilly sensations, with constant fever for two weeks, headache, and pain in the back. The *blood* showed hyaline bodies, crescentic and ovoid forms, and a few half-grown intra-cellular organisms of the tertian type. On the following day flagellate bodies were seen. The temperature was irregular, showing slight daily rises for several days. Quinine was given on the 21st, five grains every four hours, and, after this day, no tertian organisms were seen; only crescents and ovoid bodies were noted. The temperature was subnormal after the 23rd.

Case 9 (10529) has been mentioned under the cases of aestivo-autumnal fever. See page 142.

Cases of mixed Infection with Tertian and Aestivo-autumnal Organisms Observed in the Dispensary.

There were two cases of mixed infection observed in the dispensary.

CASE 7546.—A colored woman, aged 17, admitted to the dispensary on December 2nd, 1890. She complained of having had quotidian chills during August and September. Quinine was followed by relief, but, after a month, the paroxysms returned, and have recurred, she says, nearly every morning for the last six weeks. The *blood* showed a considerable number of typical tertian, intra-cellular organisms. Quinine, two grains three times a day, was given. Five days later the patient returned, stating that she had had no chills, but complained of feeling "terrible funny" at about the time when she ordinarily had the chill. The blood showed crescents and pigmented leucocytes.

This patient, who lived in an excessively malarious district, had probably been subjected to repeated malarial infection. Small doses of quinine readily overcame the tertian infection, while the aestivo-autumnal bodies resisted for a much longer time.

CASE 10351.—A man, aged 53, admitted to dispensary July 7th, 1891. He dated his symptoms back for four or five days, complaining of headache, vomiting, general lassitude, and occasional chills, fever, and sweating. The temperature at the time of admission was 102°. The *blood* showed typical aestivo-autumnal, hyaline bodies. Three months later the patient returned, giving a history of a return of his symptoms several weeks back, with daily chills for three or four days. Typical tertian organisms were found in the blood. Four days later, after the administration of quinine, five grains, three times a day, the patient said that he felt perfectly well. The blood showed no tertian parasites, but one ovoid aestivo-autumnal body.

It is probable that this case was one of fresh tertian infection on top of an old aestivo-autumnal fever.

In all these cases, then, it will be noted that, while two varieties of organisms were made out, the fever and the clinical symptoms appeared, in each instance, to be due to one particular set, that which was most strongly represented. In no case have we seen complicated temperature charts as a result. In cases 2, 3, 4, and 5, it would seem that there was probably a fresh tertian infection engrafted upon an old aestivo-autumnal fever; while in cases 6, 7, 8, and 9, the aestivo-autumnal organisms appeared to be the important group. It is interesting, in connection with this, to remember the experiments of Di Mattei, who found that on injecting blood from a case of quartan fever into one of aestivo-autumnal, the organisms injected increased in number, giving rise to clinical symptoms, while those already present showed a tendency toward diminution and disappearance. The converse was noted when aestivo-autumnal organisms were injected into a quartan case. In neither of his cases did a complicated fever chart result.

Most of these patients had been in very malarious districts, and had probably been again and again subjected to infections, and it is not unlikely that the predominating organism in each instance represented the fresher infection. Some may be inclined to use these cases as an argument in favor of the complete unity of the malarial organisms; as an argument that the tertian parasite may give rise to crescentic and ovoid forms. It is interesting, however, that, in most of these cases, not only the crescents were found after the disappearance of the tertian organisms, but also the other forms of the aestivo-autumnal parasite, forms which are notoriously more resistant to quinine than the tertian parasites. We have never seen any transitional stages between tertian parasites and crescentic or ovoid bodies, while every stage can be readily followed out in the aestivo-autumnal group. We have never seen any transitional stages between tertian, quartan, or the aestivo-autumnal organisms, nor have we met with observations which would give sufficient ground for the assumption that this could occur.

GENERAL CONCLUSIONS WITH REGARD TO TYPES OF FEVER.

In conclusion, then, we believe that we can distinguish three distinct types of malarial fever:

(1). *Tertian fever.* } Regularly intermittent fevers.
(2). *Quartan fever.* }
(3). *Aestivo-autumnal or irregular fever.*

(1). *Tertian Fever.*

The tertian type of fever depends upon the presence, in the blood, of a parasite which passes through its cycle of existence in about forty-eight hours. The segmentation of this organism is always associated with a febrile paroxysm; these paroxysms occur, with considerable regularity, at intervals of forty-eight hours, though, in many cases, there is slight anticipation or retardation. The duration of the paroxysm is ordinarily from ten to twelve hours. The onset of the fever is generally sudden, associated, in the great majority of cases, with a distinct shaking chill or marked chilly sensations. The febrile period lasts for a variable length of time, while the fall of temperature is accompanied, generally, by profuse sweating. Frequently, owing to the presence of two sets of organisms, there are quotidian paroxysms. More rarely, probably owing to the presence of more than one group of organisms, or to the fact that the organisms are not arranged sharply in groups, a more irregular, somewhat continuous fever may be seen; in these cases rest in bed and general treatment will often reproduce a true intermittent type of fever. During the period between the paroxysms the temperature is generally sub-normal. The single tertian infections, representing the mildest forms of the disease, occur, more commonly, in the earlier months of the spring and summer; the double tertian infections, which are more severe, form the majority of the cases later on. Spontaneous improvement is very common, though it is not generally permanent; more commonly, in the course of ten to fourteen days, a relapse occurs.

(2). *Quartan Fever.*

More rarely in this climate, we see fevers dependent upon the presence, in the blood, of a parasite which passes through its cycle of existence in seventy-two hours. As in tertian fever, the paroxysms are definitely associated with the segmentation of groups of the parasite. The paroxysms resemble, strongly, those observed in tertian infections, both in the manner of their onset and in their duration. Not infrequently, double or triple quartan infections may be observed, with resulting variations in the febrile manifestations. As in tertian fever, the symptoms yield rapidly to quinine, the organisms disappearing quickly from the blood.

(3). *Aestivo-autumnal Fever.*

Thirdly, we see a type of fever, occurring in the late summer and fall, dependent upon the presence in the blood of the aestivo-autumnal organism of Marchiafava and Celli. The cycle of existence of this parasite has not been followed out in an entirely satisfactory manner. We are inclined to believe that its duration may vary under different circumstances (malignity of the special parasite, different conditions in the infected individual, etc.) between twenty-four hours or slightly less, and forty-eight hours or more. This type of fever, in its pure form, is intermittent, while the paroxysms may be very similar to those of tertian or quartan fever. Commonly, however, the paroxysms show material differences; their length averages over twenty hours; the onset occurs often, without chills or chilly sensations; the rise in temperature is frequently gradual and slow, instead of sudden; the fall, likewise, occurs, often, by lysis instead of by crisis. The tendency toward anticipation and retardation of the paroxysms is much greater than in tertian or quartan fever, while, frequently, from the lengthening of one paroxysm, or the anticipation, perhaps, of another, the chart may show a more or less continuous fever. Sometimes there occurs a continued fever without sharp paroxysms. We believe that these phenomena on the part of the temperature are due to irregularities in the duration of the cycle of existence of the parasite, to the presence of multiple groups of the organism, and, often, to the fact that segmentation is going on almost continuously in the internal organs. It is in these fevers that haematuria and haemoglobinuria are seen. These infections include, also, the pernicious fevers as well as the so-called "remittent" fevers, though we believe that the great majority of cases of "remittent fever" referred to as such in this country, are not malarial in nature.

These fevers are much more resistant to quinine than the tertian and quartan infections, though, when given in sufficient doses, the specific action is always manifest, unless the case be one of pernicious fever resulting fatally before the drug has had time to act.

VII.—CONCERNING THE NATURE AND SIGNIFICANCE OF THE CRESCENTIC BODIES OF LAVERAN.

The general results of our observations of the organisms in the aestivo-autumnal fevers have been stated in our description of the parasite, in an earlier part of this paper, and, in this section, we wish more particularly, to discuss the significance of the so-called crescents, which, though they are never found at the beginning of the process, appear, in most of the cases of aestivo-autumnal fever, after a certain length of time. It will be remembered that Laveran,(15) in his original articles, believed that these crescents represented a species of cyst containing the developing parasites, which, at their full growth, were represented by motile filaments, the flagella which might frequently be seen to break forth from the round bodies into which the crescents changed. With these views Richard (26, 33) and Danilewsky (194) agree.

Richard (26) suggested that the crescentic bodies represented corpuscles containing malarial organisms which, before they had reached full development, had been caught in capillaries through which they passed with difficulty, and moulded into this shape during their passage.

Marchiafava and Celli, as late as 1884,(36) denied that these were parasites, but later on, when they had recognized the organism, their descriptions were similar to those of Laveran, excepting that (1885)(46) they denied that they were able to see a double contour. They did not agree with Laveran's conception of the nature of these bodies, denying that they were cystic in character.

Celli and Guarnieri,(95) however, describe the double contour, and note that often, on staining with methylene blue, a round body which is more deeply colored, may be seen near the middle, surrounded by the pigment, while the area about this is pale; the poles of the crescents show a marked affinity for the coloring matter. They note, also, for the first time that these crescentic and ovoid forms may show small round bodies—buds, as it were—about the periphery, one or more in number. The development of these minute round bodies, they suggest, may represent a method of reproduction. They also note the vacuolic degeneration of these crescentic forms, a process which had been previously described by Laveran.

Canalis,(104) in 1889, described the aestivo-autumnal organisms in an elaborate article which has already been referred to. He believes that there are two distinct cycles of development, the first lasting for a short time—about twenty-four hours—the parasite developing but a very small quantity, or, indeed, no pigment, and then segmenting in the ordinary manner; the second cycle lasting considerably longer—a variable length of time—and ending in the development of these crescentic and ovoid bodies. He also describes the double contour, suggesting a membrane, and notes that this is best seen in preparations several hours old, or fixed by osmic acid. He asserts that he has seen unquestionable evidences of sporulation in these crescentic and ovoid forms. He has seen round forms with or without double contour, containing eight or ten round or slightly ovoid bodies, each with a more obscure central part, while the periphery has the appearance of a double outline. Sometimes the pigment mass is in the middle, more frequently arranged in the shape of a crown at the centre or at one of the poles; at times the pigment appears to be retained in a small corpuscle; it may be seen to be extruded, contained in a protoplasmic mass; sometimes one sees groups of small bodies regularly arranged about a central pigment clump. He has never seen the whole process of segmentation, but he believes that these bodies are sporulating forms, both on account of their appearance and on account of their relation to the paroxysm. He also mentions the possibility that gemmation, as described by Celli and Guarnieri, may likewise occur as a reproductive process. After sporulation we have, again, small, hyaline, amoeboid bodies. The cycle of development varies in length, lasting generally three or four days, at least, before the appearance of crescents. He notes the constant appearance of young hyaline bodies after the paroxysms, slight though they may be. Canalis insists that this sporulation must be sharply distinguished from the processes of degeneration which one may often observe. "The evidence of this degeneration consists in the presence of bodies which have lost their yellow or ashy color, and have become more clear, sometimes refractive, having a double contour much more distinct than that of the ordinary parasites, and a substance transformed into a mass of round or irregular bodies, generally of different size, and with a single contour. If one prolongs the microscopical examination of one of these parasites, he may observe, sometimes, in the course of several minutes, the fusion of two or three of these bodies into a single globule, forming, finally, irregular masses which eventually unite, giving to the parasite an homogeneous aspect without any further trace of the small bodies. The pigment is sometimes arranged in a central crown, sometimes irregularly placed at one extremity or at one side of the body. The characteristics which distinguish this process from that of sporulation are; the refraction of the degenerating body; the inequality in the size of the spherules; the absence, in these, of a more obscure central part; their fusion into irregular masses, and finally into one amorphous mass." These forms may also be found during complete apyrexia without any following rise of temperature, or any subsequent appearance of amoeboid forms; they represent a cadaveric state.

Marchiafava and Celli,(100) in their article on the aestivo-autumnal fevers, note the double outline of the crescents, and assert that it represents a distinct membrane, though they say that, at times, it may not be very evident. They have seen pernicious forms of fever without the development of crescents. They have never seen sporulating crescents, and do not definitely commit themselves as to the nature of these parasites. They insist, however, that the crescents filled with small round bodies are simply forms undergoing vacuolic degeneration, and that sporulating forms, as described by Canalis, do not exist.

The theory of Canalis concerning segmentation of the crescentic forms is accepted by Golgi,(118) though he states distinctly that he has never seen the actual process of segmentation. He believes, however, that in patients whose blood contains these bodies, paroxysms occur at long intervals—intervals of ten, twelve, fifteen days—which are doubtless associated with the development of new forms from the crescents. He regards their presence in the blood, as does Canalis, as a constant menace of further paroxysms.

Antolisei and Angelini,(119, 131) in the clinic of Baccelli in Rome, state that they, also, have observed the segmentation of the crescents, asserting that the spores of the segmenting bodies have a distinct double outline, in contra-distinction to the simple outline of the degenerate vacuolating forms which represent the death of the parasite. Vacuolization occurs as well in the crescentic, as in the ovoid, fusiform, and round bodies. The sporulation, they say, they observed before Canalis, though Canalis anticipated them in his article. The bodies show eight or ten segments with double contour, similar to those of the parasite of quartan fever. There is no doubt, they say, as to the nature of the process. They describe the crescents in a somewhat different manner from the previous observers, believing that they possess an outer layer of varying thickness, which is colored with haemoglobin; this, they think, represents a membrane similar to that observed about the red blood corpuscle. The outer border of the double outline is the only smooth sharp line; the inner part shades gradually into the substance of the crescent. This membrane does not stain with methylene blue. The crescents, they believe, are very resistant forms which do not disappear readily with quinine, the parasite pursuing a sort of latent life and reviving again later, going on to sporulation.

Korolko(375) believes that the double outline represents a membrane derived from the red corpuscle; he states that it may be stained with eosin.

The view that sporulation occurs in the crescentic bodies is also held by Grassi and Feletti.(221, 339) They believe that the crescents, however, are a totally different variety of parasite from the small hyaline forms which appear so frequently with them; they describe them as a distinct species of organism under the name of Laverania, a division which is accepted by Sacharoff.(212, 276) They believe that the crescents are surrounded by a membrane which, like the membrane surrounding segmenting bodies, arises from the substance of the red blood corpuscle. The segmentation, they say, is similar to that in the Haemamoebae, but the resting stage is much longer, from eight to ten days, while the appearance of segmenting forms in the peripheral blood is abnormal. They doubt, seriously, whether the forms observed by Canalis, in the peripheral circulation, were true segmenting bodies. They believe that they have seen crescents with two nuclei. Later on, Antolisei (139) asserts that the crescents are not really encysted, but that there is a cutinizing or thickening of the peripheral layers of protoplasm, the same process which they believe to exist in the spores, giving them the double outline.

Thus it may be seen that, while, between Canalis, Golgi, Antolisei and Angelini, Grassi and Feletti, and Sacharoff there are some differences of opinion as to the development of these crescentic organisms, all believe that they may undergo a reproductive process—segmentation. The persistence of these bodies under quinine has been noted, and various of these observers have suggested that it is to the resistance of these encysted or, at least, protected forms of the organism that the long continuance of this type of malaria and the liability to relapses is due.

Bignami,(179) however, in May, 1889, in his work on the pathological anatomy of the pernicious fevers, suggests that this form of parasite is not a living body performing its normal functions, but merely a deviate and degenerate form which does not go on to reproduction. Bastianelli and Bignami (170) discuss this question at length. They conclude that the crescents belong to the same type of organisms as do the smaller hyaline bodies, not forming, as Grassi and Feletti and Sacharoff believe, a separate group of parasites. If quinine be given early, at the beginning of an attack of fever, the organisms may disappear before the appearance of crescents, while, if quinine be begun later on, the crescents, which appear ordinarily at about the end of the first week, may be present in the blood for a considerable length of time. In these crescents one frequently sees evidences of vacuolization, which is a degenerative and not a regenerative process.

Flagellate bodies, which they believe to be also degenerative forms, develop, often, from the round bodies. They call attention to the fact that, at the time of segmentation in, for instance, the tertian parasite, not all the organisms fulfil this process, but, as is well known, a considerable number of large swollen forms, which are usually extra-cellular, occur. When one observes these bodies, they may be traced through various changes; sometimes they undergo vacuolization; sometimes they break up into a number of smaller, extra-cellular forms, in which the pigment is usually seen after a while to become motionless, while the outlines of the body become indistinct and often irregular; sometimes they develop into flagellate bodies. These changes, they believe, are sufficiently proven to be degenerative. They note the remarkable analogy between these processes occurring in the crescentic, ovoid and round bodies in aestivo-autumnal fever and those which are seen in the large swollen tertian parasites. Here, as in the large tertian forms, one not infrequently sees vacuolization, deformation, and also gemmation or budding which they consider analogous to the fragmentation of the tertian parasite. In these forms, alone, do we see the development of flagellate bodies.

When crescents exist alone in the blood they have no influence upon the temperature or the general condition of the patient. Convalescence may have begun and may continue, after the administration of quinine has been omitted, while these bodies are yet present in the blood. The attacks occurring at long intervals, they believe to be true relapses, in no way connected with the slow maturation of the crescents. They note, with apparent reason, that these relapses are commonly separated by the time ordinarily required for the incubation of the disease; they believe that they are due to spores which have remained living in the internal organs. These views, first set forth by Bignami and Bastianelli, have been accepted and elaborated by Marchiafava and Celli,(220, 222, 245) both of whom insist that the presence of crescents, alone, in the blood has no influence upon the health of the patient. Dionisi,(173) also, in studying the blood corpuscles, notes that the presence of the crescents appears to have no influence in producing anaemia.

Mannaberg(249, 291) takes an entirely new view of the origin and significance of the crescentic bodies. He calls attention to the fact that many observers have noticed the not infrequent presence of several small hyaline bodies inside of one blood corpuscle. He insists that, in many instances, the two parasites thus included move toward one another and finally become joined together. It is a process of conjunction, of copulation. After joining together in this manner, a membrane is developed about them. The nuclei of the two small corpuscles which enter thus into copulation are close to one another, forming in this manner a pale, unstained area in the centre of the parasite, while the outer, more deeply staining part of the ecto-plasm constitutes the more deeply staining poles of the crescent. Not infrequently one may see the two small nucleoli present in the middle of the body, though these are very often hidden from view by the pigment, becoming evident only after treating the specimens in such a manner as to dissolve the pigment. Mannaberg mentions four reasons which he believes form a convincing argument in favor of his views: (1) The fact that the crescent possesses a membrane; (2) the structure of the parasite as revealed by staining; (3) the formation and arrangement of the pigment; (4) the segmentation.

(1). This is, according to Mannaberg, the one variety of the malarial parasite which possesses a membrane, a fact which proves the biological difference between these bodies and the other forms. With the other protozoa, the formation of syzygia is, also, always followed by encystment.

(2). With regard to the structure of the crescent, Mannaberg insists that when one carefully examines the body, two distinct component parts may always be made out. Celli and Guarnieri first noted that only the poles, and sometimes one or two granules toward the middle of the crescent, take on a deep color with staining fluids. Mannaberg states that "the young crescents—that is, those in which the pigment is scattered in fine granules along the whole of the body—take, on staining, a general pale color, while the poles and the zones about the border are of a slightly deeper hue. In fully developed crescents, which one recognizes by the concentration of the pigment in one or two clumps, sometimes in the middle, sometimes more toward a pole, one sees, almost without exception, the evidences of duality, in that, beside the colored poles and the border, a transverse part also, over which the pigment lies, which divides the crescent into two symmetrical halves, takes on a deep stain. It is, moreover, to be noticed that the inner parts of both constituent bodies remain almost colorless, while beneath the pigment, in the transverse bridge before mentioned, there appear two deeply-stained points. These points one rarely sees in ordinary preparations, because they are generally hidden by the pigment; but, if one dissolves this by allowing the specimen to remain several hours in weak ammonia, they may be seen in many fully-developed forms, though they may stain more faintly as a result of this treatment. Such a ripe crescent, freed from pigment, appears very like the early stages of conjunction. The slight differences between the two pictures consist in the fact that, in the crescent, the plasma mass at the point of conjunction between the two individuals (the transverse bridge) has become more marked, while the nucleoli have diminished in size and in staining propensity."

(3). With regard to the origin and arrangement of the pigment in the crescentic bodies, Mannaberg is of the opinion that "by the conjunction of the two copulating parasites, an appreciably increased vital activity develops in both of them, which manifests itself in the rapid development of pigment and the coincident decolorization of the red blood corpuscle. While the amoeboid forms are very slightly, or, indeed, not at all pigmented, there is always more or less pigment in crescents. This pigment appears in separate distinct granules and rodlets, just as in parasites of the tertian and quartan type. In fresh specimens these separate pigment granules within the crescent show slight vibratory movements. Owing to currents in the plasma they change their place slightly, and form, as a result, ever-changing groupings. In the already concentrated pigment one never sees any motion. As in the parasites of the regularly intermittent types of fever, the pigment, in the ripe crescents, becomes concentrated, but often this occurs in a manner which speaks for the duality of the crescent. Granules move from the two limbs toward the middle in such a manner that, at a certain point of time, they take an aster-like form. If the concentration proceeds yet further, we then see two clumps of pigment corresponding to the two limbs, which very frequently remain separated from one another, or finally run together into a single mass. This aster-like arrangement of the pigment is so very common that one cannot doubt that, in the two halves of the crescent, there are independent currents which cause this grouping; from this process also, then, the dual nature of the crescent makes itself evident. In those crescents in which the concentration of the pigment occurs, not in the middle of the body, but at one or the other pole, one may assume that they have arisen from the conjunction of two forms dissimilar in size."

(4). The transverse segmentation of the crescents, which has also been noted by Grassi and Feletti, Mannaberg has been able to confirm. Segmentation occurs, frequently, through the middle of the body, and, before the total separation of the two halves, these bodies may hang together like a pair of sausages. With either half, a part of the pigment remains. These segmenting bodies possess a deeply-staining granular contents. He believes that the segmentation and the deeply-staining granules which are often present in great numbers, suggest a reproductive process, yet this is not definitely proven. He believes that from the transverse segmentation of the bodies, only one conclusion can be drawn, namely, that the crescents are dual in nature. The size of the crescents, their somewhat delayed appearance in the blood, their resistance against quinine, the difference in their internal structure, are, he believes, to be explained by this view.

The process, he believes to be a pseudo-conjugation. He has not been able to determine the fate of the segmenting bodies. He does not believe in the hypothesis of Bastianelli and Bignami, that the crescentic bodies are degenerate forms. Against this argument he brings forward the fact that they are so rarely seen included in phagocytes.

Van der Scheer (356) and Laveran (350) have been unable to confirm Mannaberg's observations. The former is sceptical as to the existence of a membrane about the crescentic bodies, inclining, rather, toward the view that the double outline is due to changes occurring in the parasite after the preparation of the microscopical specimen.

Manson (347) believes that the crescent "is intended to carry on the life of the species outside the human body."

Coronado (146) holds a view different from all of the above-mentioned authors; he asserts that the crescents are empty cysts left after the escape of the flagella.

Sforza,(313) recently, in staining the parasites by Canon's method,* notes that the crescents, instead of taking up the methylene blue, show a pale rose color resembling the hue which is shown by degenerating

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* Harden in alcohol abs., 5–10 minutes.

Stain in;

Methylene blue (conc. aq. sol.)	40.
Eosin (0.25/70 per cent. alcohol 100)	20.
Aq. dest	40.

for twenty-four hours. Wash in distilled water and mount.

red blood corpuscles. He concludes that, in the crescentic bodies we are dealing with a degenerative form of the parasite "which, during its cycle of development, invades but in part the red blood corpuscle, and that the greater part of the crescentic body is nothing more nor less than the degenerate red corpuscle."

Laveran, in November, 1892,(280) and again in 1894,(360) reiterates his views concerning the crescents. He denies vigorously that they can be empty cysts, stating that he has, many times, watched the bodies after the disappearance of the flagella without ever seeing them take a crescentic form. On the other hand, he has frequently observed the transformation of crescents into round bodies, and, in turn, into flagellate forms. He says, also, that he has frequently seen febrile symptoms in patients whose blood contained crescents alone.

He has never been able to see anything which would lead him to believe that Mannaberg's theories are true. He suggests an interesting explanation of the development of crescents. The malarial parasite, he says, "is found in the blood in two principal forms; (1) amoeboid bodies in different stages of development, free in the serum, or attached to red corpuscles; (2) encysted bodies in the red corpuscles,[*] presenting first a spherical form, then a crescentic form. We have seen, above, that the encystment of the parasitic elements in the red corpuscles explains, very well, this singular crescentic form. The existence of a cystic membrane appears indubitable. These modifications of the haematozoa of paludism are more easily understood when one considers that this parasite lives in a medium the composition of which is variable; the blood of a patient who is profoundly anaemic and cachectic is very different, from the point of view of the number and the resistance of the red corpuscles, of the composition of the serum, and of the activity of the leucocytes, from the blood of an individual who, having recently arrived in a malarious district, is attacked by fever for the first time. I have shown, in my preceding communication, that crescents are seen, almost always, in individuals who are cachectic or who are, at least, markedly anaemic. It seems to me easy to comprehend that in such cases the haematozoon may develop differently than in those patients where the blood has not yet undergone profound alterations. Its presence in the form of amoeboid bodies, in the blood of these latter patients, excites a lively reaction, and the parasites, which become the prey of the leucocytes, or which are destroyed by the quinine, have not the time to become encysted. On the other hand, with the cachectic individual, the parasites develop without encountering the same obstacles. The impoverished blood is more easily overcome and the parasites become encysted." He believes that those cases where the crescents are found during what the patients believe to be the first few days of the illness, are really instances of old latent infection. The resistance of these forms against quinine, Laveran believes to be due to their encysted condition, the encysted parasites remaining a long time latent. He sums up his views concerning the crescents as follows: "The parasite of paludism develops first in the blood in the form of amoeboid bodies which live in the free state in the blood, or which adhere to the red corpuscles; generally the development of these parasitic elements in the blood provokes a lively reaction and one is obliged to interfere early and to give quinine. In these conditions the haematozoon does not arrive at its phase of encystment. On the contrary in cachectic individuals the economy, accustomed to the presence of the parasites, reacts but little, and the haematozoon can go through all its phases, penetrate the red blood corpuscles, and become encysted, all the more, because, as the patient has not had violent attacks, one delays considerably the administration of quinine."

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[*] Laveran acknowledges that the crescents may develop *in* the red corpuscle.

To sum up, then, the various views held to-day with regard to the nature of the crescentic bodies: Many observers believe that the double outline of the crescent is due to the presence of a membrane. Antolisei suggests that this is rather a condensation of the external part of the body, and not a true membrane. Laveran believes that the crescents represent an encysted form of the parasite; that they are active, indeed unusually virulent parasites, resisting, more than the others, the action of quinine; that while their mode of reproduction is not known, their presence in the blood is always the menace of a relapse; that frequently, without the presence of other forms, they may cause active febrile symptoms. Canalis, Antolisei, Angelini, and Golgi believe that these represent a more resistant form of the aestivo-autumnal organism, a form which has a cycle of development longer than that of the smaller variety, from which, however, they are directly derived. They believe that sporulation occurs in a manner similar to that in the case of the quartan parasite; that, in the blood containing this form of organism alone, the paroxysms occur at long intervals, ten, twelve, fourteen days, or even longer. Grassi and Feletti and Sacharoff believe that the crescent represents a separate and distinct type of the parasite, which they call Laverania. The former assert, also, that they have observed segmenting forms. Bignami, Bastianelli, Marchiafava and Celli believe that they are deviate and degenerate forms of the parasite. Mannaberg believes that they are encysted forms following a pseudo-conjugation of two individuals; that they can again segment into two bodies similar to the original. He does not believe that they are degenerate forms, though he has been unable to follow out their further development. Manson believes that the crescents are forms "intended to carry on the life of the species outside the human body." Coronado believes that the crescentic bodies are empty cysts from which flagella have escaped. All agree that the crescents do not appear at the beginning of the infection. Bastianelli, Bignami, Antolisei and Angelini, who have more carefully followed out their development, have shown clearly that they appear, generally, in the spleen from the fifth to the eighth day; in the blood from the seventh day on.

Our own observations with regard to the nature of the crescents have been, for the most part, already stated in the preliminary section concerning the organisms. We have noted, as well as the other observers, that, in the fresh specimen, the crescent has a somewhat refractive protoplasm, while the border shows a greater refraction, similar to that which, as Antolisei states, one observes about the border of the red corpuscle. Whether this has the significance of an actual membrane, or whether it is simply the indication of a slight cuticular thickening of the outer part of the body, we do not feel clear, though we incline rather to the latter view. We have never noted that this more refractive border or double outline showed the color of haemoglobin, though, during a considerable part of its existence, the body is probably surrounded by some corpuscular substance. In stained specimens we have never seen any tendency on the part of this outer border to take up eosin or acid coloring matters, as is the wont of bodies containing haemoglobin. We have observed, also, the fact that the poles of the crescents stain more deeply than the central part, in which there exists a clear area, and, at times, we have also made out darker staining spots beneath the pigment. We have not, however, carried out studies of stained specimens with regard to the finer structure of the parasite, with sufficient system to speak positively concerning Mannaberg's observations. We can only say, from what we have seen, that the idea that the crescent is formed as a result of conjugation, appears to us to lack confirmation. From a considerable experience in the study of fresh specimens, we can say that, while the presence of two parasites in one corpuscle is occasionally seen, it is a rather rare occurrence; that while we have seen two parasites lying side by side, as is shown in Plate II, No. 19, this has been extremely rare. On the other hand, we have been able, again and again, to trace what we believe to be every step in the formation of crescents from the bodies with pigment gathered in the centre, such as one occasionally sees at the time of the paroxysm, and we feel that there can be little doubt that the crescent develops from these bodies. With regard to the time of their appearance, the tables, which have been already given, show, in an interesting manner, how thoroughly our results agree with those of Bastianelli, Bignami, Antolisei and Angelini; these forms are not seen during the first days, but appear generally during the second or third week. Taking, for instance, the cases which were observed in the hospital, as those in which the observations were most reliable, the following table shows:

Cases observed in the first week......	35;	crescents 2;*	5.7 per cent.
Cases observed during the second week, where crescents had not been previously observed.........	35;	crescents 27;	77.1 per cent.
Cases observed after second week, where crescents had not been previously observed................	48;	crescents 35;	72.9 per cent.
Cases of doubtful duration.............	8;	crescents 5;	62.5 per cent.
Relapse of a case where crescents had been previously seen.........	1;	crescents 1;	100 per cent.

It will thus be seen that, in these instances, the percentage of cases showing crescents in the second week is even a trifle higher than in

* In both of these cases the patient had had previous attacks of malaria, and, while they stated that their symptoms had lasted only two days, it is not at all improbable that the process was a relapse from a previous attack.

the later weeks, showing, quite clearly, the time at which these bodies first appear. They are, indeed, found with nearly equal frequency from the beginning to the end of this week.

Another point that is clearly shown by our tables is the fact that, in those cases where the treatment with quinine is begun during the first week, the organisms may often disappear without being followed by the appearance of crescentic forms; thus it may be remembered that in twenty cases where hyaline bodies alone were present on admission, and treatment was begun in the first week, crescents appeared in only four—20 per cent.; in six cases, where treatment was begun in the second week, crescents appeared in three—50 per cent.; in thirty-one cases, where treatment was begun after the second week, crescents appeared in seventeen instances—54 per cent. This, again, is good evidence that crescentic bodies are not formed during the early part of the first week.

The question concerning the significance of the crescents is a much more difficult matter to decide. As we have stated, we do not believe that they are conjugate forms, as asserted by Mannaberg. They do not appear to us, from what observations we have been able to make, to represent cysts, as we cannot persuade ourselves that there is any direct evidence of their possession of a membrane. What, then, is their relation to the other organisms of this group, and what influence do they exert upon the fever? With regard to their influence upon the fever, we can only state that in 3 of the 8 afebrile cases, crescents alone were found; that while in many cases, during an afebrile period, we have been unable to find other forms in the blood than crescents, we have always, when the patients have shown febrile relapses, seen small hyaline bodies associated with them. Are we, then, to consider this a proof, as do Golgi and his followers, of the segmentation of these crescents? Are we to consider the small, fresh, hyaline bodies as the offspring of these; and are we to ascribe the febrile paroxysm to reproductive processes going on in these crescentic organisms? Or are we to believe with Bignami, Bastianelli, and others, that these resistant bodies—for resistant they surely are—are deviate and degenerate forms of the parasite?

Segmentation of the crescents we have never observed. We have, however, occasionally seen the much discussed vacuolization, as shown in the plate. This vacuolization, in the instances in which we have observed it, has been, clearly and unmistakably, a degenerative rather than a regenerative process. We have also observed the development of the small peripheral bodies, the gemmation, which has been so frequently described, a crescentic or ovoid body occasionally showing, on one side, a smaller, round, clear protrusion of the protoplasm, which may be sometimes drawn in or again cut off, so as to lie separately beside the body; this process is particularly common in the flagellate forms. We have not supposed that this was a regenerative process. And lastly, we have seen the crescents, as well as the ovoid forms, change into the round bodies, which often develop flagella. The round forms show a distinctly less sharp index of refraction, while the so-called double outline is less noticeable. We have seen, then, in the crescents, what we believe to be evidences of degeneration (vacuolization, gemmation), and we have seen, further, the change into the ovoid and round forms which we have learned to recognize as the precursors of flagellation, concerning the nature of which we shall next speak. We have never seen the transverse segmentation of Mannaberg, nor, indeed, have we ever seen any indications of segmentation, as is described by Canalis, et al. We have seen the crescents present in both the febrile and afebrile periods. When seen alone, they are rarely or never associated with fever; with the fever we always see the advent of small, hyaline, amoeboid forms. The small hyaline forms disappear quickly after the administration of quinine, while the crescentic forms remain much longer—often for weeks, sometimes for months. From practical observation, then, we can say that the crescents represent a very resistant form of the organism; that their presence in the blood alone is often unassociated with fever; that in many instances where they have previously been seen without fever, relapses have occurred, but always in association with the presence of small, hyaline and amoeboid forms; that in connection with these attacks of fever, we have never seen reproductive forms, while we have occasionally seen what we believe to be degenerating bodies; that it is clearly demonstrated that the crescents may change into the round bodies from which flagellation is frequently observed. We feel that our observations do not justify a definite conclusion with regard to the significance of these bodies.

VIII.—THE FLAGELLATE BODIES.

Concerning the significance and nature of the flagellate bodies there has been a continual dispute since the first note by Laveran.(15) Their extreme activity, the remarkable manner in which they agitate the surrounding corpuscles, the power of individual motion which the separate filaments possess, led Laveran to assume that they represented the highest stage of development of the malarial parasite. He described them in his first article somewhat as follows: In repose they are represented by a spherical body about six micro-millimetres in diameter, containing a ring of rounded pigment granules of equal size. In motion they are surrounded by, usually, three to four fine filaments in active, serpentine motion. The length of these filaments is three or four times that of the red corpuscle, possibly longer; the ends are slightly swollen. They may arise from one or from various points on the periphery of the body. The central mass, at the same time, may be in active motion, while the granules change position. The movements of the central body are like those of an amoeba. He saw filaments break loose from the body, and found them moving about free in the blood. This original description by Laveran was, at first, quite generally discredited, notwithstanding the fact that Richard, shortly afterwards, confirmed his observations. Marchiafava and Celli,(34, 35, 36) not having seen the bodies, insisted, at first, that they were not parasites but simply degenerative changes in the red corpuscles, similar to those produced by subjecting blood to a high temperature. In 1885,(41) however, when they had found flagellate bodies in four cases out of 42, they recognized their parasitic nature. Later in the same year,(45) they expressed the opinion that the flagellate forms represented a further stage of development which the parasite rarely reached. In 1886,(55) Osler described them clearly, and, in 1888, Councilman (81) noted the fact that they were much more frequent in the blood of the spleen than in the circulating blood. Excellent drawings of flagellate bodies may be found in Vandyke Carter's (70) article in 1888. Since then most observers who have been able to study the blood in malarial fever have noted these forms. They have been seen in all types of malaria, though they appear to be less common in quartan fever than they are in tertian or in aestivo-autumnal infections.

Canalis,(104) in 1889, studied the flagellate bodies with care, and notes that, in aestivo-autumnal fever, they are developed only from the full grown round forms, which, in turn, come from the crescents and ovoid bodies. He believes that they are seen, usually, several hours before the febrile paroxysm, though they may occur in apyrexia. They are more commonly found in the internal organs than in the circulating blood. They are smaller than the flagellate forms occurring in tertian and quartan fever, which, particularly in the former, may be double the size of the red blood corpuscles. They show a scant collection of granules in the centre, with a fairly clear peripheral zone, from which the filaments burst forth. After a certain length of time the movements of the pigment cease, while the granules collect in a small, dense, irregular mass; the movements of the flagella become slower and finally cease. The distinction between the more clear peripheral zone and the pigmented central area of the parasite, begins to disappear, while the entire substance of the body becomes more refractive. This is probably a cadaveric state of the flagellate body. Canalis does not commit himself as to the significance of these forms.

Golgi (118) believes that the flagellate bodies are a passing phase in the development of crescents, and rather suggests that they are degenerate forms.

Antolisei (129) believes that flagellation is a degenerative process similar to fragmentation and vacuolization. In studying the tertian parasite, Antolisei noted that the flagellate bodies develop only from the large, swollen, fully-grown forms of the organism, which either fragment, become vacuolated, or develop flagella—never segmenting. The flagella, he believes, are sarcodic prolongations of the protoplasm. He (139) states that he has seen the flagellate bodies themselves become vacuolated.

Grassi and Feletti (221) call attention to the fact that they never have observed flagellate bodies until the blood has remained twenty minutes or more on the slide. They do not believe that they are reproductive forms, but, rather, that they represent involutive or degenerative changes. They note that the nucleus does not take part in the process, neither dividing nor entering into the flagella. They mention what Councilman (81) and Marchiafava and Celli (41, 45) have also noted, that certain of these ovoid, crescentic, or round forms may show an extremely rapid undulation of the outline without the presence of flagella. They liken the process of flagellation to the development of filaments from degenerating red corpuscles.

Sacharoff,(212) in his studies on the "parasite of irregular fever" (the aestivo-autumnal parasite), is inclined to believe that the flagellate bodies develop only outside of the organism; they represent changes provoked by exposure of the blood to a low temperature. He notes, as do Grassi and Feletti, that they are not observed until about a quarter of an hour after the preparation of the blood is made. Their appearance begins, nearly simultaneously, at different points in the preparation. He has succeeded in staining the flagella by the following method: He collects a series of drops of blood on cover glasses, some of which are placed immediately in a moist chamber, while one is placed upon a slide, with vaseline at the borders of the glass, and is submitted to microscopical examination. He is able to follow the transformation of the crescents into ovoid and round bodies, the arrangement of the pigment in the shape of a crown, and, shortly afterwards, the appearance of movable filaments. After waiting a short time to allow the number to increase, he removes the cover-glasses from the moist chamber, spreads out the blood, dries, fixes, and colors with gentian violet. The filaments are intensely stained of the same color as the protoplasm of the parasite, which takes so deep a stain that the pigment granules are no longer distinct. He has published photographs (276) of these forms.

Terni and Giardina (145) observed flagellate bodies in twenty-five out of sixty-two cases of aestivo-autumnal fever; they were noted, generally, just before febrile attacks. They were always accompanied by the round bodies, from which they had doubtless developed.

Bastianelli and Bignami,(152) in their studies of the tertian and quartan infections, agree with Antolisei in believing that the flagellate bodies, as well as the large, swollen, extra-cellular forms from which they develop, are degenerative in nature. They find them most numerous toward the beginning of the paroxysm. They compare the changes in the crescents (fragmentation, gemmation, vacuolization, and flagellation), as does Antolisei, to the changes occurring in the large swollen forms of the tertian parasite, believing them all to be degenerative changes. This standpoint has since been taken by Marchiafava and Bignami.(245)

Recently (300, 301, 324) interesting studies of the flagellate bodies have been made by Sacharoff. He notes that after a short exposure to lower temperature than that of the body, the crescents rapidly change into round forms, and then into flagellate bodies. In coloring flagellate bodies after the manner of Romanowsky, and studying their structure, Sacharoff has convinced himself that "the process of formation of the flagellate bodies consists in a perversion of the karyokinetic nuclear division, in a breaking up of the nucleus into the chromatin filaments, and in the escape of these from the parasite; these filaments, which are in lively motion, represent the flagella." This, he believes, is, undoubtedly, a degenerative process, the rapidity with which it occurs showing that the crescent cannot be long exposed to cold without dying. The same process, he states, may occur in the full-grown tertian parasites and in the parasites of chronic malaria in birds, which divide in the same way—by karyokinesis.

Opposed to these views, that the flagellate forms are degenerative in nature, are a number of observers, the more important of whom are Laveran,(229) Danilewsky,(194) Dock,(151) Mannaberg,(261) Coronado (278) and Manson.(347) Laveran (229) believes that these bodies are cysts containing the fully developed flagella, which represent the parasites at their most perfect stage of development. He denies that the flagellate forms have any relation to the similar appearances produced by the action of heat upon the red corpuscles. "The differences," he says, "which exist between the flagella of paludism and the sarcodic prolongations of the normal red corpuscle, submitted to the action of heat, are numerous: firstly, the flagella of the haematozoa of paludism are seen at the ordinary temperature of the Laboratory. I have seen them frequently at a temperature not above 15° C. The sarcodic prolongations of the red corpuscle do not develop until one heats the blood to 56° or 57°. Secondly, the haematozoa have never been observed excepting in patients suffering with malaria. In the blood of these patients they are always associated with other parasitic elements, spherical pigmented bodies, from which they appear to arise. Flagella never arise from the red corpuscles, as do, always, the sarcodic prolongations which one can bring about by heating the blood strongly. Thirdly, the flagella of paludism differ from the sarcodic prolongations by their form and their dimensions, which are much more regular, and in the vivacity and the variety of their movements. None of the observers who have, themselves, seen the flagella go through their various motions, rolling and unrolling upon themselves, causing the most varied movements among the surrounding red corpuscles, which they sometimes seem to seek to pierce, would venture to assert that one could confound these movements with those of the sarcodic prolongations produced by heat. The flagella move, sometimes, so rapidly that they cause changes in the position of the spherical body to which they are attached. When they are free, they preserve the same vivacity, the same variety of movement." (Page 87.)

Danilewsky (194) holds similar views concerning these bodies.

Dock (151) suggests that the flagellate bodies "represent resting states of the organism, capable of existing independently, perhaps even of reproducing themselves, but also able, under favorable circumstances, of reproducing the typical growth of the parasite."

Mannaberg (201) takes an interesting view not dissimilar to that of Dock. He writes as follows: "In my opinion, these forms, as has been already said, are by no means to be regarded as phenomena of death ('agonieproducte'). It could hardly be explained why only a relatively small number of the parasites present show these changes when all the bodies in the preparation die in a short time. Moreover, one ought to see, here and there, flagella in the circulating blood, in which, as I shall later show, there occurs, at the time of the paroxysm, a great mortality among the parasites, dying forms being present in numbers. The same would be expected after the giving of quinine; but none of these things actually occur. Finally the remarkable activity of the movements is a convincing argument against the idea that the process is a phenomenon of the agony. My idea is, that we have, in the flagella, organs which permit the parasites to enter into a saprophytic existence. I suspect that the flagellate bodies enter upon the first steps of a cycle of existence outside of the human body, and that, as a result of the unfitting culture medium, the death of the young spores occurs." He notices, also, that they do not develop until the blood has been outside of the body for some little time.

Manson (147) believes that . . . "the flagellated organism which proceeds from the crescentic body is the first stage in the life of the malarial organism outside the human body, and the living moving flagella, into which it breaks up, the second stage. The central sphere to which the flagella are at first attached, and from which they are derived, must be looked on as residual."

Lastly, Coronado,(373) as has been stated above, in his cultivation experiments, believes that he has seen the longitudinal segmentation of free flagella into young individuals, a fact which, if true, would demonstrate that the free flagellum was a fully-developed, perfect individual.

Which of these several views are we to take? This is a very difficult matter to decide. We have observed flagellate bodies in all varieties of malarial fever. In the tertian and double tertian fevers the flagellate bodies were always noted a little before or during the paroxysm. In tertian infection, out of 174 cases observed in the hospital, flagellate bodies were noted 15 times. In quartan infection, flagellate bodies were noted in 2 out of 5 cases. In 105 cases of aestivo-autumnal fever observed in the hospital, flagellate bodies were noted 18 times. In the cases of tertian fever the flagellate bodies were noted, always, during or shortly before the paroxysm. In one instance, only, was a body seen eleven hours before the chill, and once when the temperature was normal between paroxysms. In the eighteen cases of aestivo-autumnal fever, in four cases they were seen during the paroxysm; in nine cases the temperature was normal; in three the fever was continuous; in one case the organisms were found in the spleen after death. In quartan fever the parasite was observed once several hours before a paroxysm, and once in association with degenerative forms during an abortive paroxysm. In quartan fever the flagella developed from full-grown, extra-cellular forms. In tertian fever the flagellate bodies developed, always, from the large, full-grown, extra-cellular forms, forms which are often considerably larger than the red corpuscle. In aestivo-autumnal fever the bodies developed, invariably, from the round, pigmented bodies which, in turn, could be traced to the crescents. We have never seen the appearance of flagella in bodies still contained in the red blood corpuscles.

In tertian and quartan fever, then, the process of flagellation was observed, invariably, at the time when full-grown organisms were found in the blood, at the time when segmenting organisms were to be seen—reproductive forms—but also at the time when degenerative processes—vacuolization, fragmentation—were most common. In one instance a flagellate body was seen during apyrexia, at a time when only occasional large swollen forms were seen, beyond the half developed forms within the red corpuscles, from which we have never seen flagellate bodies develop. The tertian flagellate bodies were materially larger than the quartan forms which resembled much more, the flagellate bodies in aestivo-autumnal infection. We have seen nothing which would lead us to believe that the development of flagellate bodies in aestivo-autumnal fever had any connection whatever with the paroxysm. On the other hand, in the majority of cases these forms were noted after the paroxysms had ceased, when the temperature was entirely normal. In 6* of the 18 cases of aestivo-autumnal fever quinine had been previously administered, and in seven of these instances flagellate bodies were observed for days after the fever had entirely disappeared. These statistics give us little particularly definite, then, with regard to the nature of the bodies. Their appearance, their activity, the regularity of outline, the shape of the flagella are very much against their being compared to the sarcodic prolongations of degenerating red corpuscles, which are certainly very dissimilar in appearance. Their occurrence in tertian and quartan fevers, generally in association with segmenting forms at the time of the paroxysm, might lead us to lean toward the opinion of Dock and Mannaberg, that they represent a reproductive process differing from that which usually takes place. On the other hand, the arguments of Bignami, Bastianelli, Marchiafava, Celli and others, who call attention to the fact that, in tertian fever, the flagella develop, regularly, from the large, swollen forms which otherwise end, apparently, only in vacuolization and fragmentation, and draw so interesting an analogy between these forms and the crescentic, ovoid, and round bodies, from which the flagella develop in aestivo-autumnal infections, have, also, much to say in their favor.

The most suggestive point in our analyses is, it appears to us, that concerning the time at which the flagellate bodies in aestivo-autumnal infections appear. In an half of the cases the paroxysms had ceased; in 8 out of 20 instances quinine had been previously given; that is, for days and, sometimes, for weeks after the activity of the infection had certainly been overcome, we were able to see flagellate bodies in association, sometimes, with other unquestioned degenerative changes. There is another point which has been, singularly enough, very little, if, indeed, at all, noted in the literature. Whatever our opinion may be concerning the primary influence of phagocytosis on the cure of malarial or other infections, it is an undoubted fact that any lifeless or dying foreign material in the blood current is attacked with particular activity by the phagocytes. The young intra-cellular parasites in the midst of relatively normal red corpuscles are almost never engulfed. What forms, or what constituents of the malarial parasites are most commonly attacked?

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* In both of the two additional instances in the dispensary where flagellate bodies were noted, quinine had been previously administered.

(1). Most commonly, we see the engulfing of the free pigment clumps which are left after segmentation—the lifeless pigment.

(2). Again we see the small, extra-cellular bodies, the result of fragmentation from large tertian or from quartan forms, or those half-grown forms which have burst from the corpuscle and become deformed and immovable in the field.

(3). Next in frequency, perhaps, do we see the engulfing of segmenting forms.

(4). Again, we may, in aestivo-autumnal infection, see small forms, contained in crumpled, brassy colored (necrotic) corpuscles, taken up together with the corpuscle.

All of these forms, with the exception of the segmenting parasites, are generally considered to be degenerative in nature. It is, however, to be remembered that it is at the segmenting stage that the parasite is most vulnerable, as proven by the experimental administration of quinine, while it is an accepted fact that many of the segmenting forms are, normally, destroyed in the blood serum at the time of each paroxysm.

(5). But the one form of malarial organism which one may clinically observe to be invariably, or almost invariably, attacked, is the flagellate body. Where a flagellate body is seen to develop in the field, the writers have, again and again, seen one, two, or even three leucocytes crawl into the field of the microscope and attempt to engulf the parasite, and, in many cases, the attempt is not unsuccessful. Often, to be sure, the flagella escape and the central body alone is engulfed, but in many instances the whole parasite is taken up. It is true that this argument might be used by others as indicating a special virulence on the part of the flagellate body, which would call forth an immediate attack from the protectors of the economy, but it would be interesting to find that the forms most commonly attacked were, in the one instance, the undoubted degenerative forms, and in the other the most perfectly developed full grown bodies.

Another argument in favor of the degenerative nature of these forms of the parasite is the fact of the rarity of their appearance immediately after the formation of the specimen. In our observations they appeared, always a few minutes, usually five, to ten, to fifteen, after the preparation of the specimen. We have never found them in the first few minutes of observation.

The nature, then, of the flagellate bodies does not appear to be entirely understood. There are rather strong arguments which speak in favor of the view that they are degenerative stages of the parasite, and others which speak against it. No observations have, however, been made, with the exception of the as yet unconfirmed work of Coronado, which suggest a possible function, or which tend to clear up their relation to the cycle of existence of the parasite.

While our observations concerning the time at which these bodies appear, their association with undoubted degenerative forms, their persistence after the disappearance of fever and after the administration of quinine, the manner in which they are engulfed by the phagocytes, are all, it seems to us, suggestive evidence that these bodies are degenerative in nature ; on the other hand, the extreme regularity in the shape of the flagella, their extraordinary activity, their power of individual motion, cause us to hesitate seriously in accepting this view.

We believe that the nature of the flagellate bodies is not yet clearly understood, and must be decided by future research.

IX.—THE ACTION OF QUININE ON THE MALARIAL PARASITE.

We have not made a systematic study of the action of quinine upon the fever or upon the parasites, and in this article we will only touch upon the subject. Suffice it to say that our observations have all tended to support the views first advanced by Golgi, that the time at which the malarial organism is best attacked is just at the period of segmentation.

In dealing with the tertian organism, we have found that a moderate dose of quinine, given just before the paroxysm, so that the drug may be in solution in the blood at the time of the segmentation of the organisms, is always followed by an almost complete obliteration of the group of parasites then undergoing segmentation. An excellent illustration of the effect of quinine has been shown in Case 9047, page 113. Ordinarily, quinine, gr. v–x (0.325–0.65), given at any time during the paroxysm, will be sufficient to prevent the appearance of the next chill, though not generally to completely obliterate the group of parasites. When the parasite is in the endo-globular stage (between paroxysms) quinine has relatively little effect, though in many mild tertian cases it will succeed, even in this stage, in preventing an approaching chill, if given ten to twelve hours before a paroxysm.

In quartan infections the same rules appear to hold true. In most of the tertian infections, as they occur in Baltimore, very small doses of quinine are sufficient, if the patient be kept in bed, to eradicate the fever. Thus, in most cases of tertian and double tertian fever, several days' rest in bed and two weeks' treatment with as little as gr. ii (0.13), three times a day, is followed, generally, by a permanent recovery. The organisms usually disappear from the blood within the first four days.

In the aestivo-autumnal infections, our observations concerning the time at which quinine is most efficacious are too few to justify us in expressing any opinion. We have seen no cases where, as in tertian or quartan fever, a single large dose of quinine, given at the proper time, has appeared to almost destroy the infection—at least to cause the disappearance of the fever for a considerable length of time. Here the doses of quinine must be materially larger. In most instances we place the patient simply upon quinine, gr. v (0.325), every four hours, keeping him in bed for three or four days; in the hospital for from one to two weeks. Under these circumstances permanent recovery is usual, after two or three weeks' treatment. In the same manner the cases in the dispensary, so far as we could follow them, recovered under similar doses continued through a proper length of time—two or three weeks. In severe and pernicious cases much larger doses of quinine may be necessary. In our cases we have used, generally, the muriate of quinine and urea which we have given, hypodermically, in doses as high as gr. xx (1.3). We have had no experience with the intravenous administration of the drug, as advised by Baccelli. It will not be worth while to discuss, in this paper, the value of other remedies against malaria. The only drug which deserves any serious consideration, beyond quinine and the other cinchona derivatives, is methylene blue, the value of which has been shown, by many observers, to be very slight. We see no reason to depart from the conclusions reached by one of the writers several years ago—that, while methylene blue has a certain definite action upon the malarial parasite, it is materially less efficacious than quinine, failing to accomplish its purpose where quinine acts satisfactorily; that it has no advantages over quinine which would warrant its further use.

X.—GENERAL CONCLUSIONS.

Malarial fever is rare in Baltimore during the winter months, but becomes more frequent as the season advances, reaching a maximum in the month of September, the majority of all the cases occurring in August, September, and October.

Any differences between the susceptibility of individuals of different ages, and of the two sexes, depend, apparently, only upon the varying chances of exposure to infection.

The relative susceptibility of the negro is, by nearly two-thirds, less than that of the white population.

We have distinguished three varieties of the malarial parasite:

1. *The tertian parasite.*
2. *The quartan parasite.*
3. *The aestivo-autumnal parasite.*

(1). The *tertian parasite* requires about forty-eight hours to accomplish its complete development, and is associated with relatively regular tertian paroxysms, lasting, on an average, between ten and twelve hours, associated, almost always, with the three classical stages—chill, fever, and sweating. Frequently, infection with two groups of tertian organisms gives rise to quotidian paroxysms; rarely, infection by multiple groups of organisms gives rise to more irregular, sub-continuous fevers.

(2). The *quartan parasite* is an organism requiring about seventy-two hours for its complete development. It is rare, in this climate, and is associated with a fever showing regular quartan paroxysms, similar, in nature, to those associated with the tertian organism. Infection by two groups of the parasite causes a double quartan fever (paroxysms on two days, intermission on the third). Infection, with three groups of the parasite, is associated with daily paroxysms.

(3). The *aestivo-autumnal parasite* passes through a cycle of development, the exact length of which has not, as yet, been determined; it probably varies greatly from twenty-four hours or under, to forty-eight hours or more. But few stages of development of the parasite are found, ordinarily, in the peripheral circulation, the main seat of infection being, apparently, in the spleen, bone-marrow, and other internal organs. Infection with this organism is associated with fevers varying, greatly, in their manifestations. There may be quotidian or tertian intermittent fever, or, more commonly, more or less continuous fever with irregular remissions. The individual paroxysms last, on an average, about twenty hours. The irregularities in temperature depend, probably, upon variations in the length of the cycle of development of the parasite, or upon infection with multiple groups of organisms.

We have not been able to separate two distinct varieties of the aestivo-autumnal parasite, though we feel that more investigation is needed upon the subject.

The cases of malaria in the spring and early summer are of the milder, more regularly intermittent varieties (tertian and quartan fever), the severe aestivo-autumnal infections beginning to appear only in the later summer, and reaching their maximum in September.

The colored race, while showing a relative insusceptibility to malarial infection, is equally susceptible to the various forms. The infections which occur are, however, more apt to take a simpler, milder course—the single tertian cases, for instance, outnumbering the cases of double tertian fever.

The majority of all the cases of malarial infection in this climate depend upon the tertian parasite; these tertian infections form the vast majority of all the cases in the first half year, but occur throughout the malarial season. The majority of infections during the height of the malarial season depend, however, upon the aestivo-autumnal parasite.

The earliest cases of tertian infection are more commonly single in nature, while as the season advances double tertian infections become more common.

Nothing, in our experience, has led us to believe that these varieties of the parasite are interchangeable. They are, we believe, distinct varieties, though closely allied to one another biologically. Combined infections, with parasites of different varieties, may occur, but they are rare—forming less than 2 per cent. of all the cases which we have observed.

The crescentic bodies, associated with the aestivo-autumnal parasite, develop from the small hyaline forms. We have seen nothing to support the views of Mannaberg that they are the result of conjugation. We have never seen sporulating forms which we believe to have developed from crescents. We are not, as yet, inclined to accept the view that these are degenerate forms; we believe that their true nature is still undetermined.

The nature of the flagellate bodies which may develop in all types of malarial fever, is not yet determined.

The specific action of quinine upon these three varieties of the parasite is undoubted. It exerts its influence most strongly when the parasite is undergoing the process of segmentation, before the entrance of the fresh segments into new red corpuscles. It is best administered, then, just before the beginning of a paroxysm, if we wish to obtain the greatest effect with a single dose. The action is much more rapid and certain in the tertian and quartan fevers than in the aestivo-autumnal infections.

XI.—TABLE OF REFERENCES* TO THE MAIN WORKS TREATING OF MALARIAL FEVER SINCE THE RECOGNITION OF ITS PARASITIC ORIGIN.

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(2). **Virchow.** Zur pathologischen Physiologie des Blutes. Virchow's Archiv, 1849, II, 587.

(3). **Hischl.** Über Pigmentbildung nach Febris intermitttens. Zeitschrift der k. k. Gesellschaft der Aertzte in Wien, 1850, 338.

(4). **Planer.** Über das Vorkommen von Pigment im Blute. Zeitschrift der k. k. Gesellschaft der Aertzte in Wien, 1854, 127; 280.

(5). **Ray Lankester.** On Undulina. Quarterly Journal of the Microscopical Sciences, Lond., 1871, XI, 387.

(6). **Kelsch.** Contributions à l'anatomie pathologique des maladies palustres endémiques. Arch. de Physiologie, 1875, 690.

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(8). **Lewis.** Flagellated Organisms in the Blood of Rats. Quarterly Journal of the Microscopical Sciences, 1879, 109.

(9). **Klebs** and **Tommasi-Crudeli.** Studien über die Ursache des Wechselfiebers und über die Natur der Malaria. Arch. f. Exper. Path. u. Pharmak., 1879, XI, 311.

(10). **Gaule.** Über Würmchen welche aus den Froschblutkörperchen auswandern. Archiv. für Physiologie, 1880, 57.

(11). **Dochmann.** Zur Lehre von der Febris Intermittens. St. Petersburger Med. Woch., 1880, no. 20, 164.

(11^a). **Tommasi-Crudeli.** Studi ulteriori sul Bacillus malariae. Bull. del R. acc. med. di Roma, 1880, VI, 9–12.

(12). **Tommasi-Crudeli.** Der Bacillus Malariae in Erdboden von Selinunte und Campobello. Arch. f. Exp. Path. u. Pharm., Leipz., 1880, XII, 225.

* The table is arranged, as far as possible, chronologically. A number of Russian articles of which good abstracts could be obtained were not consulted in the original. All other instances where the original articles were not consulted are mentioned in the table of literature. A few other references, unavoidably omitted from this list, will be found in foot notes. In a number of instances one article has been reproduced in several different journals or in translations without essential change. References to all these reproductions or translations will be found under that to the original article.

(13). **Tommasi-Crudeli.** Malarial fever. The Practitioner, Lond., Nov., 1880, XXV, 320.

(14). **Laveran.** Note sur un nouveau parasite, &c. Bulletin de l'académie de médecine de Paris, séance du 23 Nov., 1880.

(15). **Laveran.** Un nouveau parasite trouvé dans le sang des malades atteints de fièvre palustre. Origine parasitaire des accidents de l'impaludisme. Bull. et mém. de la soc. méd. des hôp. de Par., 24 Dec., 1880.
Also, L'union méd., Par., 10 July, 1881, no. 95.

(16). **Laveran.** Deuxieme note, &c. Bull. de l'acad. de méd. de Par., sé. du 28 Dec., 1880.

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APPENDIX.

After the greater part of this article had already gone to the press, there appeared two communications, which are of too much importance to pass over in silence. The first of these, by Di Mattei of Catania,(350) treats of the experimental malarial infections in man and animals. He publishes several new inoculation experiments in man. In his first experiment he inoculated four individuals, hypodermically, with blood from a case of quartan fever. In the first two instances, where 2 cc. were injected under the skin of the forearm, a typical quartan ague, with the characteristic parasites, appeared after an incubation period of 17 days in the first instance, and 11 in the second case. In two cases where, respectively, 1. and 0.5 cc. were injected, the result was negative. In the second experiment, a healthy individual was inoculated with blood from a case of aestivo-autumnal fever. Hyaline bodies and crescents were found in the blood at the time of inoculation. The patient suffered from epistaxis, and the blood flowing from the nose was collected in a vessel containing sterilized water at 37°. 4 cc. of a mixture containing equal quantities of blood and water were injected hypodermically. On the 15th day after the inoculation an irregular fever began, the blood showing hyaline aestivo-autumnal parasites. Eight days later crescentic bodies were found.

The author then reviews the literature of experimental malarial infection and concludes: "That the malarial parasites may be divided into several species, though in certain stages these resemble one another from a morphological point of view; that each species has for itself a special biological cycle; and that one variety never merges or changes into another. That between the several varieties of the malarial parasites and the types of fever, there exists an undeniable (unverwischbares) relation of dependence, for the former" (the parasites) "are to be recognized as the cause, the latter" (the fever) "as the effect; that, thus, one type of fever does not change into another because it is caused by a distinct variety of parasite. That in those forms of malarial fever where no ground type is to be made out, we have often to do with, so to speak, impure cases, with individuals whose system is invaded by different varieties of malarial parasites at the same time."

The author then speaks of the results of an elaborate series of studies on the experimental infection of birds with the haematozoa which so closely resemble the malarial parasites in man.

Careful estimations of the temperature in infected birds appear to show that there is no change from the normal.

Quinine, bichloride of mercury, arsenic, have no effect on the course of the infection.

In 83 attempts to transfer the infection by inoculation, intra-venous, hypodermic, intra-abdominal, intra-pulmonary, the results were all negative.

He examined the blood of doves from malarious and non-malarious districts, and studied healthy birds kept in various localities, at varying altitudes, and during the different seasons of the year, and concludes that, while infection with the haematozoa is rather commoner in summer than in winter, and in birds kept close to the ground rather than in those whose cages are hung in lofty positions, yet there appears to be no difference between the frequency of infection in malarious and non-malarious districts.

The close association of healthy with infected birds does not appear to be followed by infection; nothing in his observations suggested the possibility of hereditary infection.

In 16 cases, inoculation of birds with the blood of malarial men gave negative results.

In 4 instances the hypodermic injection of the blood of infected birds into healthy men was without effect. In one instance 1 cc. of the blood of an infected bird was injected into one of the veins of the forearm of a healthy man, but without any particular effect.

The author then compares, in the following table, the differences between malarial infections in man and infections with the similar haematozoa in the dove:

In the malarious individuol.	*In the infected dove.*
Elevation of temperature occurring as paroxysms of fever.	No elevation of temperature.
Paroxysms occurring in relation to the cycle of the parasite.	No relation between the cycle of the parasite and the temperature.
Quinine and arsenic are efficacious.	Quinine and arsenic have no action.
Local conditions are a considerable and important factor in the infection.	Local conditions have no influence.
The oft-confirmed hereditary infection.	Hereditary infection does not occur.
Artificial inoculation of an healthy individual with malarial blood always produces the infection.	Artificial infection by means of the blood from infected to healthy doves does not occur.

From these facts he concludes that the two processes are not identical; that the parasites occurring in birds, though similar morphologically, differ materially from the malarial haematozoa of man. He believes, therefore, that these haematozoa of birds should not be called "malarial."

In the second paper, Bastianelli and Bignami(358) present the results of some valuable studies upon malarial infection.

In the first part of their paper they treat of the finer structure of the parasites of the aestivo-autumnal fevers. A review of this part of their work may be found in an earlier part of this article (vid. p. 47).

Particularly interesting are their views concerning the crescentic bodies. They trace the gradual development of these forms from the small hyaline bodies; they deny the existence of a membrane.

The central chromatin spot or spots, on which Mannaberg lays so much stress, are often lacking; "usually there is a lack, then, of the structure which, in these parasites, represents the nucleus."

"In (p. 180) the body with central pigment, after the solution (fusione) of the central body" (chromatin granule), "the chromatin substance increases in a more or less marked manner, and from these forms segmentation occurs. On the other hand, in the bodies not destined to sporulate (semilunar phase of the parasites) the dispersion of the chromatic granule of the protoplasm takes place as in the others, but, with the ulterior development, the nuclear substance does not increase. This is not an hypothesis. We have, in fact, seen that the young form of the semilunar phase has more chromatin than the adult form, indeed the adult forms are the paler the more voluminous they are.

"But we already know that with all malarial parasites the chromatic substance increases with the increase in volume, especially just before division. In the forms of the semilunar phase the contrary occurs. So, then, by this fact also, as well as for the reasons to which we have given utterance elsewhere, we may arrive at the conception that the crescents are sterile forms of the aestivo-autumnal parasites."

Mannaberg's idea that the crescents are conjugate forms, they believe to be without foundation.

With regard to the biological significance of these bodies, they assert that in several unicellular parasites belonging, especially, to the coccidia, the existence of two cycles of development has been demonstrated. One cycle is accomplished during the ordinary life of the parasite. But after the parasite has lived, as such, through a series of generations, there begins a second cycle of existence, which is represented by forms which cannot terminate their development unless in the external air or in the tissues of another animal. If these forms of the second cycle do not escape from the body of the animal in which they are formed, they remain sterile and, after a certain time, degenerate and die. So many facts of this nature have been recently discovered that it appears not improbable that this may be a general law for this class of endo-cellular parasites.

It appears probable to the authors that these parasites, which develop in a closed cavity and cannot reach the external air, have a phase of life which represents a rudiment of this second cycle.

Being deprived of the possibslity of completing the cycle, they have lost, also, the power to reach the complete development that belongs to the other forms of this second cycle in other closely related organisms. "The semilunar phase of the malarial parasites represents an abortive phase, sterile, of that cycle of development which, in closely related parasites, is completed only in the external air (ambiente). The analogy is also found in the fact that the forms of this abortive phase make their appearance only after a greater or less number of generations which have passed through only the ordinary cycle of the parasite."

They then pass on to consider certain points in connection with phagocytosis. Golgi(309) has recently advanced the hypothesis that the entire cycle of development of the parasite may be passed through while it is yet contained within a phagocyte. Bastianelli and Bignami assert that, with the exception, occasionally, of spores, all included parasites are rapidly destroyed unless they be contained in red blood corpuscles. If this progressive growth of the included bodies occurs, they believe that one should find all stages of development, with equal frequency, within the phagocyte. But this is not the case. While the included parasites may be in every stage of development, certain forms are found with much greater frequency than others. The youngest forms are, for instance, rarely seen, while the older are more common; facts which, they believe, are strong evidence against Golgi's idea.

The second part of their paper is devoted to a consideration of certain lethal infections with but few parasites.

They assert that if one takes into consideration the number of parasites in the whole system, not only in the peripheral blood, there exists, always, in pernicious fever, a considerable number of organisms. They have never observed a case of pernicious fever where the diagnosis was not to be made by the examination of the peripheral blood. They take up those acutely fatal cases with marked cerebral symptoms which, at autopsy, show evidences of but a slight or, indeed, of an old cured malarial infection, in association with cerebral hyperaemia, pulmonary hypostaxis and haemorrhages, the other organs showing no grave degenerations. These cases, which occur almost invariably, at the hottest season of the year, often in individuals who work in the fields, they believe to be very possibly instances of isolation and not due, as some have supposed, to an unusual toxicity of the parasites.

Another section of the paper treats of the period of incubation of the experimental malarial fevers, and of the nature and origin of the recrudescences and relapses.

They report four new cases of experimental infection with the aestivo-autumnal parasites.

In the first case the injection (how made?) consisted of 2 cc. of blood; irregular fever with the typical parasites appeared two days later.

In the second case, where the parasites were few, 5 cc. were inoculated with exactly the same result.

In the third case, ¾ cc. of blood produced fever in five days; the inoculated blood contained but few organisms.

In the fourth case, where $\frac{1}{10}$ cc. of blood, containing a fair number of parasites, were inoculated, the incubation period lasted four days.

From a table of all observations which they have collected, they conclude that the time of incubation in the several varieties of fevers varies as follows:

	Maximum. (days)	Minimum. (days)	Mean. (days)
Quartan fever..............................	15	11	13
Tertian fever..............................	12	6	10
Aestivo-autumnal fever..................	5	2	3

The cases of Antolisei and Angelini,(111) Sacharoff,(334) and Di Mattei,(358) where the incubation period for aestivo-autumnal fever was materially longer, are not included in this list. The periods of incubation in these cases were respectively 9, 12, and 15 days. In the first of these cases, however, the parasites were only scanty in the inoculated blood (only crescents were seen); in the second, they had been four days in the body of a leech on ice; in the third, the blood was mixed with sterilized water.

The authors conclude that "the period of incubation with one variety of parasites varies inversely with the quantity of material inoculated."

The period of incubation represents "the time necessary for the inoculated parasites to reach, by multiplying, the quantity necessary to determine the fever." . . . .

"The mean and minimum periods of incubation, under similar conditions, vary in the various groups of fevers: it is least in the aestival fevers, longer in the tertian, and still longer in the quartan." . . . .

"The period of incubation in experimental malarial infection is not a constant quantity, but varies in the same group of fevers and in different groups of fevers. In the same group of fevers it depends chiefly on the quantity of the inoculated material. In different groups of fevers it varies with the rapidity of the cycle of development of the parasite and with the special capacity for reproduction of the parasitic variety."

The ordinary recurrences and relapses, the authors ascribe, as they have before, to the fact that certain spores which have escaped destruction, continuing their development, begin again to multiply, increasing until the parasites have reached a number sufficient to produce fever. The length of time separating the relapse from the last attack depends on the number of organisms which have escaped destruction.

Those relapses which do occasionally occur at intervals of weeks or even months from the primary attack, the authors can explain only by the hypothesis advanced first by Bignami, that certain spores which have been included by phagocytes remain a long time living. These bodies, they assert, certainly retain their form and staining properties for some time, even if they do fail to show any sign of a membrane; if they be not spores, in the proper sense of the word, yet they have some properties which seem to indicate that they possess a greater resistance. The writers state, however, that nothing appears to them "a priori contrary to the hypothesis that, of these so-called spores of malaria, some, born like all the rest without membrane, may finally acquire one." These bodies, then, might lose their staining properties and, being so small and perhaps scanty, they might escape notice. To their ultimate development, then, the relapses might be ascribed. In some sporozoa, for example, the *Benedina octopiana*, similar processes occur; the spores are born without membranes, which they afterwards acquire, losing at the same time their staining properties.

Lastly, the writers report an interesting case of grave malarial infection presenting the syndroma of Dubini—the so-called "Electric Chorea."

The most interesting points, it appears to us, in this paper, are the views advanced concerning the crescentic bodies.

Most authors have interpreted Bignami's original assertion,(179) that the crescentic bodies were "forms of a deviate and interrupted evolution (forme di evoluzione deviata e interrotta)," as an indication that he considered them degenerative in nature. The present theory, it is interesting to note, is similar to that recently advanced, independently, by Manson, who believes that the crescents are forms "intended to carry on the life of the species outside the human body."

DESCRIPTION OF THE PLATES.

The drawings* were made with the assistance of the camera lucida from specimens of fresh blood. A Winkel microscope, objective, 1/14 (oil immersion), ocular, 4, was used.

Figures 4, 13, 23, 24, and 42 of Plate I were drawn from fresh blood, without the camera lucida.

PLATE I.

THE PARASITE OF TERTIAN FEVER.

1 —Normal red corpuscle.

2, 3, 4.—Young hyaline forms. In 4, a corpuscle contains three distinct parasites.

5, 21.—Beginning of pigmentation. The parasite was observed to form a true ring by the confluence of two pseudo-podia. During observation the body burst from the corpuscle which became decolorized and disappeared from view. The parasite became, almost immediately, deformed and motionless, as shown in Fig. 21.

6, 7, 8.—Partly developed pigmented forms.

9.—Full grown body.

10–14.—Segmenting bodies.

15.—Form simulating a segmenting body. The significance of these forms, several of which have been observed, is not clear to the writers who have never met with similar bodies in stained specimens so as to be able to study the structure of the individual segments.

16, 17.—Precocious segmentation.

18, 19, 20.—Large swollen and fragmenting extra-cellular bodies.

22.—Flagellate body.

23, 24.—Vacuolization.

THE PARASITE OF QUARTAN FEVER.

25.—Normal red corpuscle.

26.—Young hyaline form.

27–34.—Gradual development of the intra-corpuscular bodies.

35.—Full-grown body. The substance of the red corpuscle is no more visible in the fresh specimen.

36–39.—Segmenting bodies.

40.—Large swollen extra-cellular form.

41.—Flagellate body.

42.—Vacuolization.

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* The writers desire, here, to express their gratitude to Mr. Broedel for his admirable work.

PLATE II.

THE PARASITE OF AESTIVO-AUTUMNAL FEVER.

1, 2.—Small refractive ring-like bodies.

3–6.—Larger disc-like and amoeboid forms.

7.—Ring-like body with a few pigment granules in a brassy, shrunken corpuscle.

8, 9, 10, 12.—Similar pigmented bodies.

11.—Amoeboid body with pigment.

13.—Body with a central clump of pigment in a corpuscle, showing a retraction of the haemoglobin-containing substance about the parasite.

14–20.—Larger* bodies with central pigment clumps or blocks.

21–24.—Segmenting bodies from the spleen. Figs. 21–23 represent one body where the entire process of segmentation was observed. The segments, eighteen in number, were accurately counted before separation, as in Fig. 23. The sudden separation of the segments, occurring as though some retaining membrane were ruptured, were observed.

25–33. Crescents and ovoid bodies. Figs. 30 and 31 represent one body which was seen to extrude slowly and, later, to withdraw two rounded protrusions.

34, 35.—Round bodies.

36.—"Gemmation," fragmentation.

37.—Vacuolization of a crescent.

38–40.—Flagellation. The figures represent one organism. The blood was taken from the ear at 4.15 p. m.; at 4.17 the body was as represented in Fig. 38. At 4.27 the flagella appeared; at 4.33 two of the flagella had already broken away from the mother body.

41–45.—Phagocytosis. Traced by Dr. Oppenheimer with the camera lucida.

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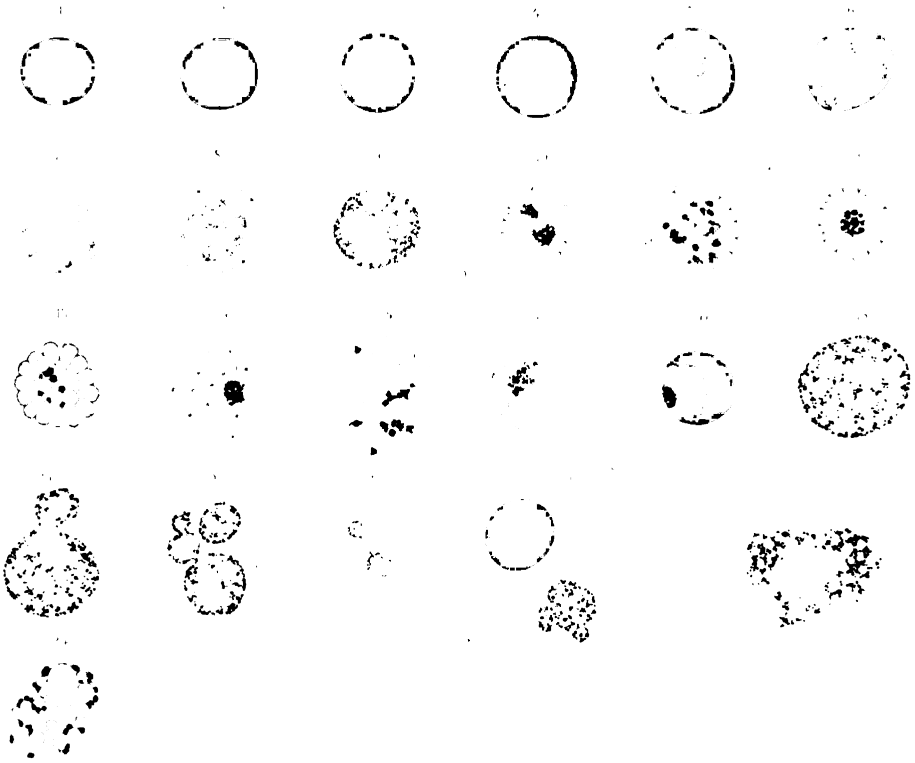
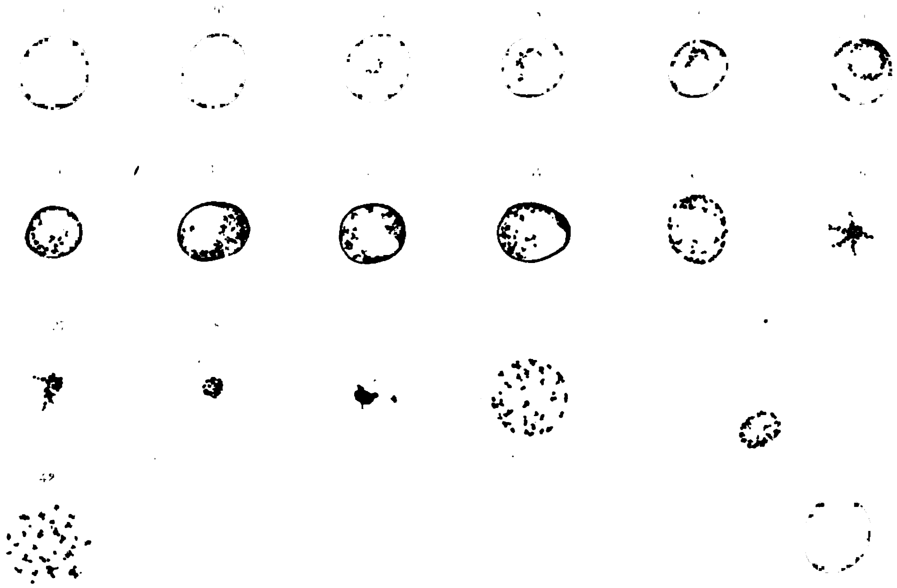
* It is unfortunate that the plate does not contain a few examples of larger forms with central pigment blocks. The writers have drawings of several as large as the segmenting body in Fig. 21.

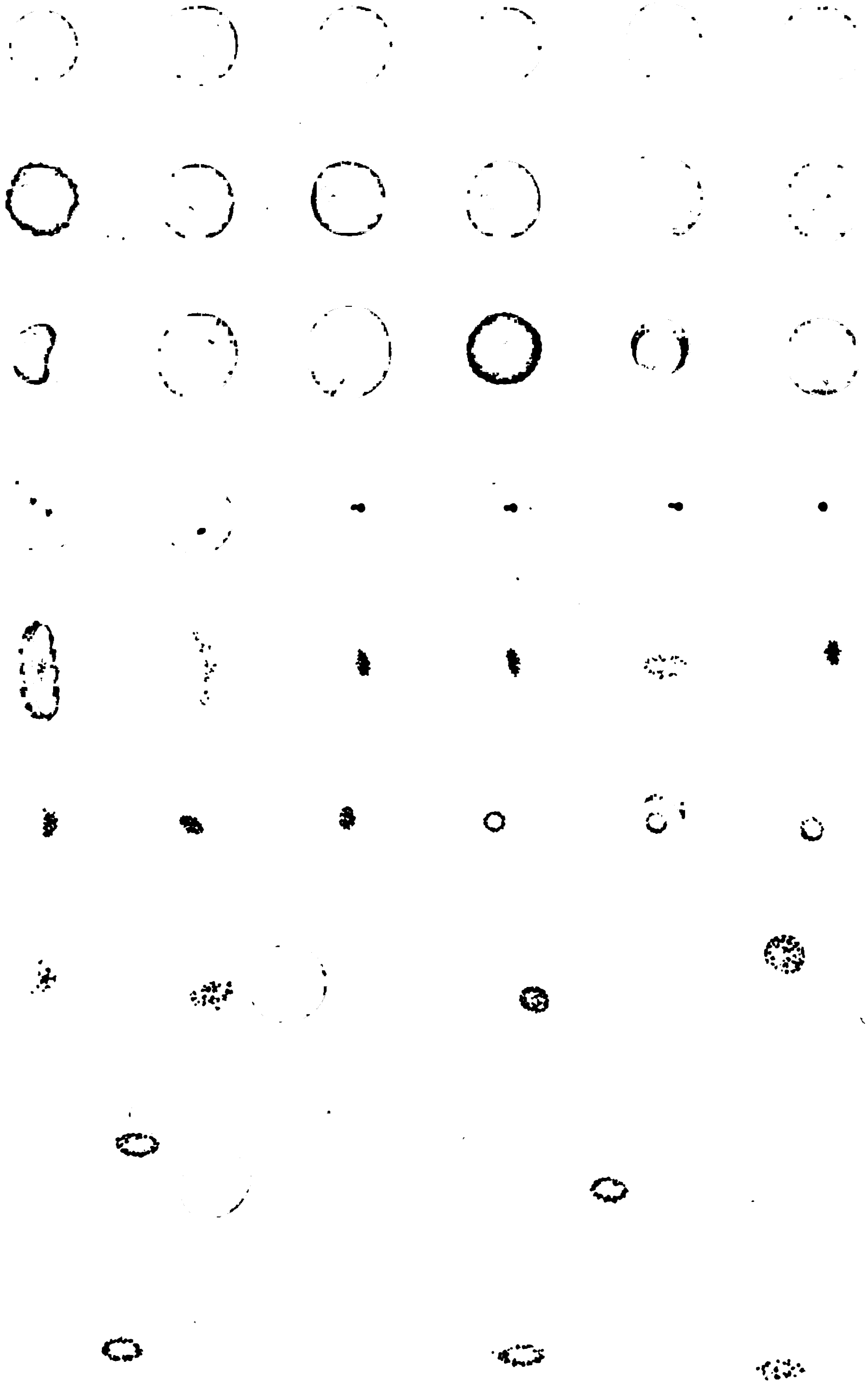
The Parasite of Tertian Fever



The Parasite of Quartan Fever.



The Parasite of Aestivo Autumnal Fever.



A STUDY OF SOME FATAL CASES OF MALARIA.

By LEWELLYS F. BARKER, M. B., Tor.,
Associate in Anatomy and Assistant Resident Pathologist.

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I.

INTRODUCTION.

The material for the following study was derived from the bodies of patients coming to autopsy in the Pathological Laboratory of the Johns Hopkins University and Hospital between 1889 and 1894.

For the permission to study the tissues and to extract protocols from the post-mortem records I have to thank Professor W. H. Welch; the clinical histories of the cases have been put into my hands through the courtesy of Professor William Osler.

Since the discovery of Laveran's parasite which rendered possible under ordinary circumstances the early recognition of a malarial infection by means of the microscopical examination of the fresh blood, it has become a comparatively rare occurrence for a patient to die of this disease. The study of the pathology of malaria is consequently limited to the few instances in which the patients die from traumatism or from some inter-current disease, and to those rare cases of pernicious malarial infection which terminate fatally.

The tissues from the cases referred to in this paper were hardened some in alcohol, some in Müller's fluid, and others in Flemming's solution. For general study the tissues fixed in strong alcohol served best, while for the investigation of certain points those fixed in Flemming's solution gave excellent results, those preserved in Müller's fluid being the least satisfactory. The tissues were imbedded in celloidin and in paraffin. For staining haematoxylin and eosin, alum-cochineal, safranin, gentian violet, aqueous magenta, Weigert's fibrin-stain and the triple stain (Ehrlich-Biondi) were employed, while for the study of the pigments and of the iron-containing compounds derived from the red blood corpuscles certain sections were treated with ammonium sulphide and others with hydrochloric acid and ferrocyanide of potassium[1] (method of Perls).

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[1] Concerning the reactions for iron and the unsatisfactory nomenclature of iron-containing compounds, cf. article by J. J. Abel, Virch. arch., Bd. 120, p. 204; also articles by A. B. Macallum, Proc. Roy. Soc., &c.

In order to determine accurately the relation of the parasites and pigments to the tissues many sections both stained and unstained were examined in media of different refractive power. For this purpose water, glycerine, balsam, a saturated solution of acetate of potassium, Farrant's medium, and solutions of chloral-hydrate were employed.

The enormous strides made in late years in the clinical studies of malaria has rendered a re-working of the pathology highly desirable. The majority of the investigators have contented themselves with the study of the blood taken from the peripheral circulation, or from that obtained from tappings of the spleen made during life. Some however, among them Bignami, Marchiafava, Guarnieri and Golgi in Italy, Metschnikoff, Laveran, Kelsch and Kiener in France, and Osler, Councilman, Abbott and Dock in America have made contributions to our knowledge of the pathology of the affection as it concerns the internal organs of the body.

In this report will be found the clinical histories of four cases of malaria, in three of which the parasites were of the aestivo-autumnal and in one of which they were of the tertian type, together with a description of the pathological findings in each. As an appendix are added certain observations dealing with the unequal distribution of the parasites in the body, and with phagocytosis in malaria.

II.

CASE A.—*Aestivo-autumnal malaria; anomalous symptoms during life.*

L. K., aet. 81, was admitted to Prof. Osler's wards July 18, 1889, complaining of pains in the head and of coldness and numbness of the feet and hands. Had in earlier life been always healthy, and on admission was a healthy-looking vigorous man for his age. On July 9th, while engaged in berry picking in a field in Anne Arundel Co., Md., he suffered from heat stroke, remaining unconscious for two hours and having to be carried to his home. The next day he was up and about again, and felt able to work, but had not been altogether well since, having suffered from headaches and occasional chilly sensations.

On admission the following note was made: "Healthy looking, much sunburnt, pulse full, walls of blood vessels soft, no oedema of feet. The lungs are clear in front and behind; the expiration is a little prolonged. The apex beat of the heart is neither visible nor palpable, the sounds are weak, the second being scarcely audible at the base. The area of liver dullness is reduced. The spleen is not enlarged; the urine is light yellow in color, specific gravity, 1010; no albumen, no casts."

Concerning the further progress of the case, we have the following account from Prof. Osler.

"I saw the patient only during the first four days of his stay at the Hospital, and thought that he was suffering from the effects of a sunstroke. He was given a tonic mixture. The patient's temperature was normal, but on the 20th and 21st the morning records were 97.6° and 97.8° respectively.

On the 25th, at 11.30, he had a chill; the temperature rose to 105° and remained high all the afternoon. At 7.30 p. m. it was again 105°, and he was given a graduated bath.

Throughout the 26th the temperature fell, but did not go below 101°; the pulse was rapid and feeble.

On the 27th the temperature at 8 a. m. was 100.5°; in the afternoon it rose to 103°, and in the evening was 100.3°; pulse, 104, extremely irregular and intermittent. There were feeble râles, with a high pitched percussion note in the right infra-scapular region. Towards evening the patient sweated profusely and the breathing was of the Cheyne-Stokes type.

On the 28th the temperature fell rapidly, sinking from 103° at 4 p. m. of the 27th to 97.3° at 8 a. m. of the 28th, and to 95.5° at 10 a. m. The pulse was extremely feeble and irregular. He vomited twice. There has been no expectoration. The breath sounds at the right base have been very feeble. Throughout the afternoon of the 28th the temperature rose and at 8 p. m. was 100°.

On the 29th the Cheyne-Stokes breathing persisted, and the patient had slight diarrhoea. His speech was disturbed but he appeared to be conscious. Throughout the 30th, 31st and August 1st he sank gradually and died on the morning of the 2d.

I did not see the patient from the date of his chill until the morning of the 2d, just before his death. The case was regarded as one of low anomalous pneumonia. The day after the chill it is stated in the note that the blood was examined with negative results; but there is no initial to indicate by whom the examination was made."

Autopsy.—(Professor Welsh.) (Abstract from the records of the Pathological Laboratory).

Anatomical Diagnosis.—Malarial fever, with malarial parasites in the blood and spleen; soft, swollen, pigmented spleen; pigmented and myristicated liver; pulmonary emphysema; general muco-purulent bronchitis; pulmonary oedema; catarrhal colitis.

Exterior.—Body, 168 cm. long; much emaciated. Hernial tumor in each groin. Rigor mortis well marked. Livor mortis in dependent parts. On belly and chest are a number (20–30) dark red liver spots, slightly elevated, which do not disappear on pressure.

Abdominal Cavity.—Loops of small intestine lie loosely in the hernial sacs which open by wide mouths at internal inguinal rings into the peritoneal cavity. Spots of fibrous thickening on peritoneum covering mesentery of small intestine. Old pigmented patches on pelvic peritoneum. Firm old adhesions binding tightly together the under surface of the liver and gall-bladder with the adjacent parts of the duodenum and ascending and transverse colon. The capsule of the liver along its anterior border and on the adjacent convexity is opaque, white, thickened and wrinkled, owing to old fibrous thickening. The diaphragm on the right side reaches the lower margin of fifth rib, on left, lower margin of sixth rib. The peritoneal cavity contains about 50 cc. of clear yellowish serum.

Thoracic Cavity.—The anterior surface of the pericardium, save a triangular area much smaller than normal, is covered with the emphysematous lungs. There are old fibrous adhesions between the pleural surfaces of the posterior parts and apices of both lungs. On anterior surface of middle lobe of right lung are some old white fibrous nodules, the size of a pin's head and larger. There is a small amount of clear serum in each pleural cavity and also in the pericardial cavity.

Heart.—Weight, 290 grams; small; myocardium of a deep brown color; some thickening of aortic and mitral valves along lines of closure, but apparently not enough to interfere with the functions of the valves. Some atheromatous deposits in pockets of aortic valves. Endocardium of left ventricle thickened and opaque. No fibrous patches in myocardium except at tips of musculi papillares. Chordae tendineae of mitral valve somewhat thickened and retracted. The coronary arteries present near their origin moderate atheromatous thickening, and are rather tortuous. Loose dark red clots and some decolorized post-mortem clots in both ventricles.

Lungs.—Markedly emphysematous, swollen, not collapsing readily, of a soft cushiony feel, air cells in anterior part of lungs near inner margin reach size nearly of pins' heads. Considerable pigmentation with coal. On section the dependent parts of lung are much congested and there is moderate general oedema. Both large and smaller bronchi contain much muco-pus, which can be squeezed out in opaque thick whitish drops. The bronchitis is general. The pulmonary parenchyma everywhere contains air. There is no pneumonia. On pleura at apices of both lungs are some old fibrous scars and immediately beneath the pleura are a few old black calcified nodules the size of split peas.

Spleen.—Weight, 192 grams; length, 13 cm.; width, 8 cm.; thickness, 3.5 cm. The capsule is extensively thickened and opaque, and the organ is surrounded by old fibrous adhesions. The consistence is soft, the organ being almost diffluent on section. Color, dark brown or blackish-brown. Malpighian bodies not readily distinguishable in the soft dark-colored pulp.

Kidneys.—Surface smooth, save some indication of foetal lobulation. Capsules not adherent. Cortex measures 6 mm. in thickness; striae distinct and regular. Weight of each kidney 196 grams. Dimensions, 10 x 5 cm. There is a small white fibroma the size of a split pea in cortex of left kidney. Adrenals apparently normal.

Bladder.—Contains about 5 cc. of whitish fluid. Mucosa normal. Prostate moderately enlarged and contains many corpora amylacea.

Liver.—Weight, 1650 grams. Dimensions, 24 x 15 x 6.5 cm. Capsule opaque and thickened along anterior margin. Prevailing color on section brown or bronzed. Centers of acini of a reddish brown, peripheries of a lighter brownish color. The gall bladder contains a moderate amount of brownish yellow bile; bile duct patent.

Pancreas.—Firm, pale, normal.

Large Intestine.—Rectum contains very hard, yellowish scybala coated with mucus. Balls of firm yellow faeces in colon and caecum. Mucous membrane of large intestine, particularly of sigmoid flexure and colon, coated with firmly adherent, stringy, very tenacious, white mucus, often peculiarly arranged in irregular anastomosing lines. The mucus is about of the consistence observed in the discharges of mucous or membranous diarrhoea.

Small Intestine.—Contains fluid or semi-fluid yellow material and presents areas of hyperaemia and of coating with mucus.

Stomach.—Contains a little partially digested food. Mucous membrane of pyloric region coated with a thin layer of mucus. On anterior wall, 4 cm. from pylorus, is a mucous polypus 6 mm. long, and 4 mm. thick, with a smooth, round extremity; not constricted at base. Near base of polypus is a round depression with smooth edges and floor communicating with an oblong depression by a narrow similar but elongated depression. The round depression is 3 mm. in diameter, the oblong measures 4 x 2 mm. These depressions extend in depth to about that of the mucous membrane. The floor of the depressions looks as if covered with smooth mucous membrane. There is no stellate cicatricial tissue in or near these depressions, nor is there any evidence of change on the outer surface of the stomach.

Brain.—Arteries of base very atheromatous; considerable increase of cerebro-spinal fluid; white substance of hemispheres presents numerous puncta vasculosa. Brain otherwise appears normal.

Microscopical examination of blood from finger shows a few pale bodies of shape and size of red corpuscles or larger, containing pigmented plasmodia; also free round pigmented corpuscles, the pigment in molecular movement (varying in size from blood plate to twice this size); also pigmented crescents, the pigment in a ring in the middle; in one specimen of splenic pulp two actively moving free flagella. In the capillaries of the brain are a few pigmented corpuscles.

Examination of the hardened tissues.—A microscopical study of the organisms and tissues confirms the findings at autopsy and the diagnosis of an aestivo-autumnal malarial infection. The unequal distribution of the parasites and especially the accumulation of immense numbers of them in the capillaries of the mucous membrane of the stomach render this case of more than ordinary interest.

The Liver.—On examination with very low powers (8 to 16 diameters) there are very few pigment masses large enough to attract notice; in marked contrast to what could be observed with these powers in the liver of Case C (tertian infection).

With higher powers intravascular phagocytes, especially macrophages, are seen to be comparatively few in number. The malarial parasites are not especially numerous in the liver. They vary in size, and have a yellow tint in tissues hardened in Müller's fluid; some contain almost no pigment; others contain very fine granules of brownish black pigment; still others contain distinct dark central blocks of pigment. A few of the organisms appear to be free in the blood or included within red corpuscles. The majority are inside mononuclear leucocytes; a few have been taken up by polynuclear leucocytes. The latter cells also contain free pigment in granules and blocks. There is marked participation of the endothelial cells of the capillaries of the liver in the phagocytic process. These cells, the cells of Kupffer and the intracapillary macrophages contain a few parasites, pigment in granules and in blocks, infected and non-infected red corpuscles, fragments of corpuscles, and particles of irregular size and shape that yield the blue iron-reaction. Some of the phagocytic cells, especially the endothelial cells, contain *brassy* corpuscles (globuli rossi ottonati of the Italians). From many of the pigmented capsules in the larger cells fine lines of yellowish brown pigment can be seen radiating out into the protoplasm. The pigment is chiefly situated in cells at the periphery of the lobules. In certain areas bright yellowish pigment in considerable quantities can be seen running along the rows of liver cells. The liver cells themselves are large, swollen, finely granular and often vacuolated. The nuclei of the liver cells vary in size and in vesicularity. The central veins of the lobules and the neighboring capillaries are dilated and the liver cells near them contain brownish pigment. The spaces between the liver cells and the capillary walls are exaggerated. Some of the liver cells themselves contain malarial pigment. No areas of necrosis can be made out, but as no tissues from this case were preserved in absolute alcohol small necroses could easily be overlooked. There is a slight excess of lymphoid cells in the portal spaces, and a few larger pigmented cells are present in the connective tissue of these spaces.

The Spleen.—The blood vessels are distended, especially those of the pulp. In places there are actual haemorrhages into the pulp tissue, and numerous red corpuscles can be made out among the cells of the pulp-cords. The capsule of the spleen is slightly thickened and the stroma is denser than normal. There is an astonishingly large number of organisms present. These vary in size, and are of the aestivo-autumnal variety, the majority appearing to be nearly full grown. They are not numerous in the larger vessels of the spleen, but are very abundant in the blood of the smaller vessels of the splenic pulp.

A large number of well formed organisms, infected corpuscles, remains of organisms and corpuscles, and fine and coarse pigment are contained within phagocytes. The macrophages are of about the same size or a little larger than those described in the liver. Many of them contain *brassy* corpuscles. The endothelial cells and the cells of the splenic pulp itself, as well as the mononuclear leucocytes, contain foreign products. Here and there a large vesicular parasite with very little pigment is visible, and a few crescents can be made out, although they are probably much more numerous than the study of hardened tissues alone might have led us to infer. They were present in considerable numbers in the fresh blood taken from the spleen at autopsy, but on account of the deformity resulting from hardening and the pallor of the bodies of these forms, we have experienced the same difficulty in recognizing them in sections which has attended the studies of other observers. The pigment is mainly contained in the splenic pulp; the Malpighian bodies are comparatively free from it, and when pigment is to be made out in the latter, it is usually included within large cells around the arterioles.

The Kidney.—There is a moderate degree of chronic diffuse nephritis, some of Bowman's capsules showing slight fibrous thickening. The glomeruli for the most part fill the capsular spaces. A moderate amount of pigment is to be seen within the glomeruli, chiefly contained in the endothelium of the glomerular capillaries; some of it being within mononuclear cells inside the capillaries. The endothelial cells of the intertubular capillaries and of the small veins contain occasionally at the poles of their nuclei granules and masses of malarial pigment. Occasionally inside the vessels a mononuclear cell containing one or more tolerably well preserved organisms can be made out. No parasites were seen in the kidney outside of phagocytes. The epithelium lining the convoluted tubules is swollen and filled with fine granules. Some of the cells are actually necrotic, the nuclei refusing to stain. A number of the tubules in the cortex contain within the protoplasm of their lining epithelium masses of bright yellow pigment. Occasionally hyaline casts are met with in the collecting tubules.

The Stomach.—The findings in the sections of the stomach are of interest. The capillaries and veins of the mucous membrane are widely dilated, many of the larger and smaller veins being engorged with red blood corpuscles, whose outlines are perfectly well preserved, and in certain areas inside nearly every red corpuscle is a parasite with a central block of brownish black pigment. Along with these masses of infected corpuscles there are often found numerous mononuclear macrophages crowded with blocks of malarial pigment like that to be seen in the infected corpuscles. There are places where the lumina of the veins appear to be narrowed near the base of the mucous membrane and as though blocked with macrophages damming back infected corpuscles. The arteries and veins of the submucosa are singularly free from infected corpuscles. The distribution of the parasites in the capillaries is very irregular; while in one area all of the capillaries may be closely crowded and distended with infected corpuscles, in other places quite near by the vessels may be almost entirely free from them. Besides the macrophages already described there are large red-corpuscle-carrying cells within the veins and capillaries, filled with blood corpuscles which stain intensely with eosin. These cells contain large single nuclei which often send out processes among the red corpuscles in the protoplasm. Some of the smaller vessels appear to have their lumina entirely filled with huge cells of the kind described, forming veritable casts. These cells must exercise considerable influence in obstructing the on-flow of blood. The surface of the mucous membrane in many places refuses to stain, and fragmented nuclei are visible evidences of superficial necrosis.

The Heart.—There is an excess of brown pigment at the poles of the nuclei of the muscle cells; otherwise there are no striking alterations.

Cerebrum.—Only an occasional infected corpuscle can be made out within the capillaries; a few of the endothelial cells lining the capillaries are phagocytic. Portions were saved from only one or two parts of the cortex.

Thyroid Gland.—In the vessels of this organ as elsewhere in the peripheral circulation it is rarely that infected red blood corpuscles are to be seen.

III.

Case B.—*Aestivo-autumnal malaria; grave abdominal symptoms.*

John B., age 34, admitted to the Johns Hopkins Hospital, September 10th, died September 16th, 1890. The following is Prof. Osler's clinical note of the case:

"I saw him in the dispensary at 1.30 p. m. He was very weak and tremulous, with eyes congested, cheeks flushed, and with a dazed, stupid appearance. The tongue was swollen, heavily furred and indented. He looked like a man who had been drinking, and I told his brother that it would be impossible for us to admit him to the wards in his present state. He assured me, however, that he had not been drinking to excess, and on ascertaining that there was not the slightest trace of alcoholic odor in the breath, I signed the order for his admission.

The following history was obtained. Family and personal history good. The patient is a sailor by occupation, and has enjoyed excellent health; he left Boston for Savannah five weeks ago; spent a week in the latter place, and as the weather was oppressive he, with several of his shipmates, was in the habit of sleeping on the grass all night. He remained well on the voyage to Baltimore, where he landed August 31st. He was about the house all the week, though not feeling quite himself, but the present illness dates from Sunday the 7th, when, without any chill or fever, he began to have vomiting. He felt extremely weak and prostrated, so that he could not get up on Monday morning. Throughout Monday and Tuesday the vomiting continued at intervals and he was completely prostrated. He had no chills, but on Monday and Tuesday he took some quinine pills. In the dispensary, after failing to detect any alcoholic odor in his breath, and on learning that he had recently come from the South, the blood was at once examined; large numbers of Laveran's organisms were found, which rendered the diagnosis clear. His temperature on admission into the ward was 101°, pulse 104, small, tension not increased, radials not stiff. The abdomen was soft; nowhere tender. The edge of the spleen was just palpable on deep inspiration; upper border of dullness at the ninth rib.

Apex beat of heart in 5th interspace within nipple line; sounds clear; examination of the lungs negative.

Blood.—Small intra-corpuscular forms in extraordinary abundance, often 6 or 8 to be seen in the field of the $\frac{1}{12}$ im. The majority of them are not pigmented and undergo very rapid changes in outline. The pigmented forms have the granules more concentrated than is usual in this stage of the evolution of the parasites. An unusual number of the leucocytes present pigment granules.

11th. Very bad night; much vomiting; temperature sank to 98.6° at 10 p. m., and to 98.2° by 8 a. m. At the morning visit the patient looked depressed; tongue heavily furred; pulse 80, small and thready; respirations 20. Had no headache and complained chiefly of profound weakness. At noon the temperature began to rise and at 4 p. m. reached 102.2°, and for 6 or 8 hours remained about 102°, gradually falling through the early morning hours and at 8 a. m. reaching 98.5°. The blood condition remains practically about the same.

12th. 10 a. m. Patient passed a better night. The vomiting has stopped but the tongue is still furred; no increase in the splenic dullness. The bowels have been freely opened. He still looks depressed and dull, and complains of a feeling of great prostration.

13th. Temperature has been about 98° for the past 24 hours, pulse 72, small. The vomiting has not been so distressing, and he has taken the milk and brandy better than on any day since admission. The blood examination shows a marked diminution in the number of corpuscles containing the plasmodia, the diminution being doubtless due to the influence of the quinine.

14th. Temperature has been subnormal, not rising above 97.5° all day. The vomiting has returned, and for the first time the vomitus contained blood, not in large amount, but sufficient to color the fluid. His mind is perfectly clear, and his sole complaint is of the extreme depression.

15th. 10 a. m. Patient's condition is worse since 8 p. m. last evening. The temperature has been below 97°, and at 12 midnight sank to 96°; pulse, 64; respirations, 20. Tongue still swollen, heavily furred and indented. Note on the blood to-day is: "plasmodia very much diminished in number. Leucocytes still show much pigmentation." The urine is amber colored, specific gravity, 1010; acid, contains a slight amount of albumen. At 9 p. m. I made the following note: "Patient is in a very peculiar condition; is drowsy, dull, roused with difficulty, and does not answer clearly. He has behaved oddly all day, and has been very restless. There has been very little vomiting; temperature has been subnormal, and is now 96.5°. For the first time the tongue is distinctly dry."

16th. Through the night the patient was very restless and had much hiccough; was not delirious, but acted queerly. The temperature sank through the night, and at 2 a. m. was 96°; at 4 a. m. the thermometer could not be made to register more than 95°, and the temperature remained at this point until 10 a. m. The vomited matter last night contained flakes of blood enough to tinge the whole fluid. He had retention of urine and this morning 1500 cc. were withdrawn, which showed a narrow ring of albumen and contained hyaline and granular tube-casts. The nurse says that he does not understand questions, but he seemed to recognize me, and gave fairly rational answers, but complained of great oppression in the abdomen. The pulse is 72, and considering his condition the volume and tension were remarkably good. At 6 p. m. I made the following note: "Temperature has risen through the day and is now 97.2°. The tongue is dry, pulse 96, regular and of very fair volume. He is extremely restless, and his face has a dusky hue; the respirations are at times gasping, 24 to the minute. He answers questions, but talks and rambles in an incoherent way. To-day very few red blood corpuscles have been found containing plasmodia; the leucocytes are still much pigmented." Patient became much more restless, threw himself about on the bed, then became unconscious, and died at 8 o'clock. The treatment consisted of half-drachm doses of quinine every six hours, which was given hypodermically when the vomiting became excessive.

Autopsy 15 hours after death.—Body 161 cm. long, well nourished, post-mortem discoloration of dependent parts and of face and neck. Peritoneum smooth, a little darkened and slaty in appearance, no excess of fluid in abdominal cavity. No pleural adhesions; pericardial and pleural cavities dry. Right side of heart distended with fluid blood; left ventricle empty and contracted. Heart valves all normal except for slight atheroma at attached borders of aortic cusps. Myocardium pale, otherwise normal; left lung crepitant, anteriorly and in lower part of upper lobe congested and oedematous. Right lung still more oedematous, deeply engorged at base. A small piece cut from extreme posterior part of lower lobe on this side sinks in water. The bronchi contain frothy mucus.

The Spleen and Liver.—The spleen measures 8 x 13 cm., is extremely soft, almost diffluent. The pulp is of a dirty brownish-red hue; the capsule is thin and shows a few superficial hemorrhages. The liver is large, slate-gray in color; its capsule is slightly thickened and opaque. Just above the gall bladder on section the substance is moderately firm and has a uniform bronze or slaty tinge. The outlines of the lobules are not well defined. There is deep pigmentation about the portal canals and the smaller bile ducts are distended.

The Kidneys are large and swollen; the surfaces are mottled. The capsules are adherent in places. On section the consistence is firm. The Malpighian tufts are prominent and congested; the medullary rays are pale and between them the lines of vessels are deeply reddened. No areas of opacity are visible. The cortex is distinctly though slightly pallid. The adrenals show no marked alteration.

The Stomach.—Contents are liquid and of a yellowish color. The mucous membrane has a slatish-grey tint, and on the anterior surface near the lesser curvature are the scars of two small ulcers and on the posterior wall three other flat cicatrices are visible. The bile duct is patent and the portal vein is free. The contents of the small intestine are reddish-brown in color, the mucous membrane is congested in places. Peyer's patches are not swollen, although the lower ones have a shaven beard appearance. The colon is deeply congested in places and covered with tenacious yellow faeces. There is no intestinal ulceration.

The Brain.—The dura presents on its surface well back on the right side a small hemorrhage. The pia over the cortex is smooth, in it, over the middle of the first right frontal convolution close to the longitudinal sinus, is an area of brownish-black pigmentation about 1 cm. in diameter. The membranes and vessels at the base appear normal. On section the substance of the brain looks natural except for turgidity of the vessels.

Microscopical Examination.—*The Liver.*—The malarial pigment is situated chiefly in the outer half of the lobules and is principally enclosed in cells. The liver capillaries are engorged with blood. In some of these many of the red corpuscles contain malarial parasites which vary in size from extremely minute forms to larger bleb-like organisms almost as large as the corpuscles. Some of these parasites contain only a little fine pigment; others none at all. Some of the liver capillaries are quite free from parasites, while others are crowded with organisms each containing a central block of brownish-black pigment. A few of the intra-corpuscular organisms not enclosed in phagocytes show fine lines of yellowish pigment granules radiating from them, which appear sometimes to extend beyond the limits of the corpuscle in which they are contained. Most of the organisms are contained within cells. In this case the endothelium of the hepatic capillaries and the cells of Kupffer have played the greatest rôle in the phagocytosis. There are some large mononuclear intra-vascular phagocytes, but most of the organisms and the remnants of organisms are contained within the protoplasm of the endothelial cells, being often, though not always, situated at the poles of the nuclei. In the intra-capillary macrophages, which are of smaller size than those occurring in the liver of Case D, the nucleus is frequently surrounded by black pigment blocks. The swelling of the endothelial cells of the capillaries is marked, being sufficient, one would think, to offer serious impediment to the progress of the blood. The liver cells themselves are swollen and granular, and many of them are filled with yellow pigment masses. In places they are atrophied and the capillaries in the atrophied areas are correspondingly dilated.

The Kidneys.—All the blood vessels of these organs are dilated, the veins of the pyramids being especially wide. There is irregular dilatation of the glomerular capillaries. Comparatively few parasites are present in the kidneys, although some distinct forms are visible within the veins and capillaries. A small number of phagocytic cells can be seen (intra-vascular phagocytes and endothelial cells). The capsules of some of the glomeruli have undergone fibrous thickening; in places the capsular endothelium is proliferated. The epithelium of the convoluted tubules is swollen and granular, and there are numerous hyaline casts to be seen in the small collecting tubules. In the pyramids haemoglobin casts can be made out.

The Brain.—A few infected corpuscles can be seen within the blood vessels. Here and there a phagocytic endothelial cell occurs. In one spot there is a very small infarct showing necrosis of the cerebral tissue, hyperaemia at its margin, and an accumulation of mono- and polynuclear cells. There are no other marked changes.

No other tissues were saved from this case. This is unfortunate, since from the grave gastric symptoms observed during life an examination of the contents of the capillaries of the mucous membrane of the stomach would have been interesting (vide Case A).

IV.

CASE C.—*Acute aestivo-autumnal malaria; death from accident; acute necrotic lesions in the liver and spleen. Remarks on the relation of malaria to cirrhotic processes.*

R. G., aet. 22. Pole, single, laborer, admitted to Prof. Osler's wards October 5th, 1892. He complained of chills and fever, and on entrance was suffering from a paroxysm, during which his temperature reached 106.8° F. He had been working at Locust Point (a part of the city near the harbor in which malarial infections frequently occur) when he was taken ill, two weeks before his application to the Dispensary for treatment. On admission his blood was examined and found to contain only a few hyaline intra-cellular parasites.

The physical examination of the heart and lungs yielded no abnormal signs. The respirations were hurried, the pulse was frequent and slightly dicrotic. The lower edge of the spleen could be easily palpated, reaching a point two fingers-breadth below the costal margin. The liver dulness was not increased. The patient vomited everything taken into the stomach, including the quinine administered, so that other methods of exhibiting it had to be resorted to. On the next day the blood was carefully examined twice, but no malarial parasites could be found. The leucocytes were not increased in number. The patient complained of severe abdominal pain on the following day; two slides of blood were examined in the early morning but no malarial parasites could be found. The patient met with an accident, associated with profuse hemorrhage, and died in the afternoon.

At the autopsy, which was made by Dr. Flexner while the body was still warm, the typical lesions of an acute malarial infection were found. There were numerous ecchymoses scattered over various parts of the skin and over the serous membranes. The muscles were brownish-red in color. The lungs were moderately pigmented; the heart valves were normal. Heart's flesh pale. Anterior mediastinal glands softened and reddened.

Liver.—Weight, 2200 grams; surface smooth; substance of a dark brown color; consistency soft; lobules invisible.

Spleen.—Weighed 800 grams; measured 23 x 11 x 5 cm.; diffluent; deep dark red in color; Malpighian bodies visible; pulp abundant.

Pancreas and *kidneys* normal; *stomach*, *intestines* and *bladder* normal. Lymph glands in hilum of spleen and about the pancreas swollen, softened and deeply congested. Culture tubes of agar-agar inoculated from various organs at the autopsy remained sterile.

The Spleen: Microscopic Examination.—The lesions in this organ resemble much those seen in certain acute bacterial infections. The organ, especially the pulp, is markedly hyperaemic. In places there are evidences of extravasation. On examining the pulp with higher powers the contents of the capillaries and veins are seen to be complex. Besides large numbers of ordinary red blood corpuscles there are a number containing malarial parasites of the aestivo-autumnal type. The majority of the latter, however, are enclosed within mononuclear cells. Well preserved organisms are by no means numerous and the contents of the phagocytes consist largely of remains of malarial organisms and shrunken corpuscles containing more or less brownish-black pigment. The number of red blood-corpuscle-carrying cells is much increased; huge cyst-like cells, usually mononuclear, the nucleus sometimes having radiating processes which run out toward the periphery of the cells, are seen sometimes containing thirty, forty, fifty or more apparently well preserved red blood corpuscles which stain deeply in eosin. The pulp cells themselves are large and swollen, and frequently contain within their substance other cells, chiefly with nuclei of the lymphoid type; sometimes also polynuclear leucocytes, and very often a number, five, ten or even more completely colorless red blood corpuscles. These cells contain in addition infected red blood corpuscles, free malarial parasites, the more or less broken down remains of parasites and free malarial pigment often arranged in dotted lines. Besides these large mononuclear cells in the vessels there are very many small and large lymphocytes seen crowding the lumina of the vessels. There are also a few polynuclear leucocytes, some ordinary large mononuclear leucocytes, and an occasional giant cell with budding nuclei, resembling those normally present in the bone marrow. The protoplasm of many of the cells in the pulp-cords stains deeply in eosin. Sometimes the protoplasm of these cells is highly refractive and the nucleus does not stain at all, or it may be broken up into a number of fragments irregular in size and shape. In these cells one or more polynuclear leucocytes are often to be seen, the hyaline protoplasm being sometimes closely crowded with them.

In some places in the pulp there are actual focal necroses, very much like those which are to be seen in typhoid fever. In these, particularly in the more recent ones, large necrotic cells with hyaline protoplasm and fragmented nuclei can be made out along with lymphoid cells, polynuclear leucocytes and endothelioid cells. In the larger necroses the necrotic cells may be almost entirely obscured by the collection of lymphoid cells and the leucocytes with polymorphous nuclei. In these areas there is evidence of division by amitosis with distortion of the nuclei (abschnürungsvorgänge), and scattered among the cells a number of minute nuclear fragments are visible. There are also in these areas large phagocytes containing within their protoplasm malarial parasites and pigment, polynuclear leucocytes, intact and broken down red blood corpuscles and nuclear fragments.

The endothelial cells lining the vascular spaces are evidently phagocytic. They contain within their protoplasm, usually at the poles of the nuclei, the remains of malarial organisms, broken down blood cells, free malarial pigment, and irregular masses of blood pigment which yields the blue iron reaction. The Malpighian corpuscles themselves are swollen; there has been proliferation in the lymphoid cells. Among the lymphoid cells can be seen a few large cells resembling somewhat the cells of the pulp, often containing within them mononuclear and polynuclear cells, red blood corpuscles, and sometimes malarial organisms and malarial pigment. These are best studied in specimens stained with methylene blue and eosin. Numerous capillary thrombi can be made out scattered through the spleen; these thrombi resemble closely those seen in the liver of this case. One is tempted to think of a relation existing between these capillary thrombi and the focal areas of necrosis.

The Liver.—The capillaries generally are dilated, in some areas more markedly than in others. Within the capillaries are many red blood corpuscles, a few red blood-corpuscle-carrying cells, lymphoid cells, small and large, a few polynuclear leucocytes, and in some parts of the liver large phagocytes. The latter may contain within their protoplasm, besides well formed malarial parasites of the aestivo-autumnal type, shrunken remains of parasites, fine malarial pigment, red corpuscles, particles of haemosiderin, lymphoid cells, and occasionally polynuclear leucocytes. The endothelial cells lining the capillaries are in places much swollen, their nuclei are large and vesicular, and within their protoplasm are sometimes visible the same substances as those mentioned as occurring within the intra-vascular phagocytes. The endothelial cells are so much swollen in places that they materially narrow the lumina of the capillaries. The spaces between the capillary walls and the liver cells are wider than normal and there is a considerable degree of atrophy of the rows of liver cells. The liver cells contain an excess of brownish-yellowish pigment. Some of the liver cells have giant nuclei. The cells of Kupffer, between the capillary walls and the rows of liver cells, are swollen and some of them are evidently phagocytic. Occasionally lymphoid cells are visible in the spaces between the capillary walls and the liver cells. The findings within the lumina of the hepatic capillaries are of interest. The number of cells with nuclei of the lymphoid type is astonishing. Many of these are of the size of ordinary lymphocytes, others being somewhat larger. Occasionally cells containing basophilic granules within their protoplasm are visible within the capillaries, and in one or two instances they are seen included within the protoplasm of makrophages. In one section two or three cells within the capillaries possessed budding nuclei quite like those of the giant cells in normal bone marrow. One of these of large size appeared to be acting as a phagocyte as it contained within its protoplasm malarial pigment and a single mononuclear cell. Some of the phagocytes which are partially or completely necrotic are surrounded or invaded by leucocytes with polymorphous nuclei. A number of the endothelial cells are also degenerated or necrosed. Single and multiple liver-cell-necroses occur scattered throughout the section, forming necrotic areas of varying sizes, sometimes as large as those seen in typhoid fever. When one or two liver cells only are necrotic the lesions are tolerably distinct. The nuclei of the necrotic cells are fragmented or absent and those of the neighboring liver cells may be shrunken and deeply stained. The protoplasm of the cell is hyaline, stains deeply in eosin, and may be invaded by polynuclear leucocytes.

In larger areas the pictures are more complex and somewhat difficult to explain. The necrotic liver cells have either been removed or are obscured by the accumulation of other cells. In these foci usually, however, the remains of liver cells and of their nuclei are visible, especially in the periphery. Accumulated here are a number of cells with small sharply stained nuclei, lymphoid cells, polynuclear leucocytes, and spindle-shaped cells with vesicular nuclei. In addition there may be large phagocytic cells containing lymphoid cells, polynuclear leucocytes, red blood corpuscles, nuclear fragments, and sometimes malarial pigment. It is no easy matter to decide as to the origin of all these different cells, although with thin sections and careful study the source of most of them can be made out. It is not always possible, however, to say what are endothelial cells and their derivatives, and what are to be regarded as blood cells and their derivatives. Some of the small deeply stained nuclei are probably to be looked upon as the offspring of leucocytes which have divided *in situ* by amitosis, as the nuclei of these cells show various distortion processes (abschnürungsvorgänge). Sometimes a cell with hyaline protoplasm and a degenerating nucleus can be seen surrounded by a number of cells whose protoplasm overlaps and seems actually to be mingling with the protoplasm of the degenerating cell, although on close focusing the boundaries of the various cells can usually be made out. The cells inside necrotic cells frequently show fragmented nuclei and hyaline protoplasm. The number of cells inside a single dead liver cell varies. In one the nuclei of ten foreign cells, most of them polynuclear leucocytes, were included, and the nucleus of one of these latter was fragmented.

There are numerous thrombosed capillaries to be made out in thin sections (vide Plate V, Fig. 1). Sometimes a single capillary appears to be occluded, and a few leucocytes with distorted nuclei are seen lying in the thrombus. In other places two or more neighboring capillaries are plugged, and in addition to the white cells in the thrombus, leucocytes, mono- and polynuclear, can be seen aggregated in considerable numbers in the neighboring capillaries. There may be a diminution in size, evidences of degeneration, or a total disappearance of neighboring liver cells. Plate V, Fig. 2 shows the condition better than any description. The occurrence of so many of these thrombosed capillaries in the same sections with the areas of focal necrosis is suggestive, and one is very much tempted to look upon the larger areas of necrosis as advanced stages of a process which began with capillary thrombosis.

The triangular portal spaces present a very peculiar appearance. The connective tissue is crowded with cells containing nuclei of the lymphoid type so that the tissue reminds one of the structure of ordinary lymphoid tissue. In the adventitia of the portal vein contained apparently in loose spaces are very many lymphoid cells. The portal veins show in section many mononuclear and a few polynuclear leucocytes, besides many makrophages such as have been described in the splenic veins and in the liver capillaries. There were no lesions of tuberculosis anywhere in the body, and no bacteria were demonstrable by cultural methods or in sections of the organs.

The Kidney.—The lumina of the convoluted tubules in the labyrinth are wide, and the projecting epithelium lining them is somewhat swollen. The glomeruli do not completely fill the capsular spaces; in some of the latter coagulated albumen may be seen. Some of the tubules in the medullary rays contain in their lining epithelium yellowish pigment. The kidney is almost free from malarial organisms and from malarial pigment, although occasionally a brownish-black particle is visible in a glomerulus.

The Mesenteric Lymph Glands.—The lymph sinuses, especially in the medulla, are wide and are filled with cells. These cells for the most part irregular in shape contain vesicular nuclei and an abundant protoplasm which stains in eosin and they resemble in general the endothelial cells which normally lie upon and are wrapped around the reticular framework. There are also many large and small lymphocytes and a few red blood-corpuscle-carrying cells. Some cells like those filling up the lymph sinuses can be seen among the lymphoid cells in the lymph follicles and cords. They occasionally contain within their protoplasm malarial organisms and their remains.

This case, it would seem, may be of help in explaining the relation of malaria to cirrhosis of the liver and allied diseases.

Even in the early descriptions of malaria the important influence of the disease as a causative factor in the production of chronic interstitial inflammations of some of the internal organs, and especially of the liver and kidneys is mentioned. Frerichs and Lanceraux both believed in a chronic hepatitis of paludal origin. Kelsch and Kiener working at the disease without any appreciation of the importance of the malarial parasites laid stress upon the changes in the liver secondary to malaria and describe both parenchymatous and interstitial forms of hepatitis. They refer to three varieties of the latter and discuss at length the character and distribution of the lesions in the liver. These same authors describe two main types of chronic disease of the kidneys dependent upon malaria, the first, a diffuse malarial nephritis or glomerulo-nephritis, and the second, a nephritis characterized by a small granular kidney. Bartels, Rosenstein, Bouillaud, and others had early referred to the relation existing between malaria and chronic disease of the kidney. Laveran emphasised a chronic interstitial pneumonia of malarial origin, and Durozier in 1870, and also Kelsch and Kiener referred to the frequent occurrence of vegetative or ulcerative endocarditis in chronic malaria and believed that the lesions of the heart valves might be directly referable to the action of the malarial poison. Finally, chronic degenerative and fibroid processes in the spinal cord and brain have been attributed by some authors to malaria.

On the other hand, by not a few authors the possibility of cirrhotic processes being due to malaria has been stoutly denied. It has been justly claimed that in many of the cases reported as instances of chronic inflammation due to malaria insufficient attention has been paid to the possible responsibility of other etiological factors, such as alcoholism, syphilis, and tuberculosis.

Dr. Osler has particularly pointed out the difficulty of saying in a given case of cirrhosis of the liver or kidneys that malaria has been the cause, and in his experience the association of malaria with cirrhosis has been very uncommon. Dr. Welch has seen only one case of malarial cirrhosis of the liver in New York, and that was in an Algerian.

The foregoing study has, however, convinced me that there are conditions present in malaria which are generally recognized as being capable of giving rise to chronic fibroid processes, and it would be strange did the latter not occur more or less frequently. Bignami in a very careful study of chronic malarial cases in Italy has come to a similar conclusion and traces with much acumen the chain of events from the onset of an acute malarial infection to the development of a cirrhotic process.

A careful consideration of the various phenomena associated with acute malaria will show that there are many ways in which a chronic interstitial inflammation could arise. Thus looking upon the chronic interstitial inflammations as being due most often to a primary degeneration of certain of the tissue elements, the new growth of fibrous tissues being secondary, we can think of many possible causes of the former. Thus, the profound changes in the character of the blood serum consequent upon the alteration and destruction of large numbers of red blood corpuscles and leucocytes, the intermittent hyperemia in the viscera, the setting free of the malarial pigment, and the accumulation of the latter in the cells and tissues, the multiple capillary thromboses which sometimes occur, the disturbances of digestion in many of the cases, the areas of necrotic cells which can be demonstrated in liver spleen and kidneys, these are sufficient to convince one of the existence of many possible injurious influences.

The evidences in favor of the idea that the parasites produce definite toxines and that large quantities of these are set free during segmentation after each paroxysm is already considerable. The clinical phenomena in general and especially the increased toxicity of the urine after the paroxysm would seem to point to this. It must be remembered, however, that as yet no toxine has been proven to be formed by the parasite. It matters little, however, whether the toxic substances are produced by the parasites directly, or are in part the indirect result of their action upon the red blood corpuscles, the white cells or tissue juices. There is sufficient evidence that some toxic agent is at work. The cloudy swelling seen in the organs, the fever, the acute splenic tumor, but more especially the actual necroses early demonstrable under the microscope, make it impossible to doubt this fact.

In our description of Case C we have referred to the extensive focal necroses in the liver and in the spleen. Single cells, small groups of cells and quite large areas of cells were found in a state of hyaline necrosis where the nuclei refused to stain and the protoplasm showed an increased affinity for acid dyes. In such necrotic areas numerous cells were present, some of them leucocytes with polymorphous nuclei, others small mononuclear cells. In some of the older ones spindle-shaped cells could be seen. Fragmentation of nuclei and phagocytosis were visible, and there were multiple capillary thrombi to be made out. We have referred to the extensive necroses of the spleen pulp cells, of the red blood corpuscles and of the leucocytes. In many bacterial infections similar areas of necrosis have been proven to be due to the toxines which the bacteria produce. Reed for typhoid fever and Welch and Flexner for diphtheria have shown that the soluble products of the bacilli alone circulating in the blood are capable of giving rise not only to diffuse parenchymatous changes, but also to definite focal lesions, areas of cell-death of varying size. Later Flexner, experimenting with blood serum, has shown that the serum of one animal will produce focal necroses in the liver kidney and spleen of an animal of a different species when injected intravenously into the latter. He further proved that these focal necroses could later result in the production of chronic interstitial processes in the liver and kidney.

In the liver, following the necroses, there was such an accurate reproduction of the cirrhosis seen in human beings that, as he put it, "a separate description seems superfluous." Areas of newly formed and forming connective tissue proceeded from the portal spaces, and also from the capsule; these were irregularly distributed throughout the organ. Newly formed bile ducts were numerous; but what was of particular moment was the association with these of another process, namely, acute degenerative changes in the liver substance which were distinctly to be recognized as the starting places of the cirrhotic processes. "The necroses and disintegration of the liver cells with emigration of the leucocytes went directly over into the new growth of fibrous tissue. New fibrous tissue could be formed within lobules, apparently independently of the inter-lobular connective tissue and of the capsule, just as there are independent foci of necroses in this situation."

It is easy to understand how the normal serum of the individual could be altered by the disease so as to become definitely toxic. Aside from the increased toxicity of the serum due to the presence of malarial toxines, the destruction of large numbers of red blood corpuscles and the setting free of young parasites, of pigment, and of masses of haemoglobin, cannot fail to be of considerable import. And although there is no experimental evidence bearing on this point, it is not impossible that the *isotonie* of the blood serum could be so affected as to lead to serious alterations not only in the constituents of the blood but also in the cells of the organs. That haemoglobinaemia and haemoglobinuria occur sometimes in malaria is well known. Haemoglobinaemia alone can give rise to an acute splenic tumor, or to an acute nephritis, as is well known in cases of poisoning by the chlorate of potassium and in the intoxication of one animal by the blood serum of an animal of a different species. The alterations in the functions of the spleen, liver, and alimentary canal could easily lead also to important changes in the blood serum.

The relations of the melanaemia to cirrhotic processes is worth considering. The malarial pigment tends to accumulate in the periphery of the hepatic lobules and in the trabeculae of the spleen. It remains, too, for some time after the infection has disappeared, and it is not impossible that the irritation caused by the presence of this pigment could give rise to a chronic interstitial inflammation, perhaps analogous to the pneumonoconioses. It seems less probable, however, that the pigment is responsible for a new growth of fibrous tissue than that the latter is secondary to degeneration due to toxic effects.

It has been generally believed that any pathological condition which leads to an intermittent hyperemia of an organ may give rise to a chronic interstitial inflammation. In malaria there can be but little doubt that there is variable hyperemia of the liver and spleen with the paroxysms, just as the size of the spleen and liver varies in recurrent attacks of malaria.

The capillaries in the liver spleen and kidney are frequently found dilated especially in certain areas. Whether this is at all dependent on the distribution of the makrophages it is difficult to say.

Finally the influence of the disturbances of the digestive processes in malaria must not be omitted in considering the etiology of cirrhotic inflammations. There is general obstruction in the tributaries of the portal vein, and this alone would suffice to materially alter the assimilation. But in addition, as we have seen, the vessels of the mucous membrane of the stomach and intestines may be occluded in certain cases by thrombi of parasites or of infected red corpuscles. In some instances the nutrition may be so interfered with that the mucous membrane becomes necrotic. Undoubtedly in such instances substances absorbed from the lumen of the alimentary canal are far from normal.

There can be no doubt, considering the comparative rarity of cirrhosis following malaria, that the individual pre-disposition must be an important factor in those cases in which it occurs. Associated alcoholism or arterio-sclerosis for example might render the tissue cells less resistant to the poisonous substances, whatever they may be, or prevent the normal processes of repair.

That there may be different kinds of cirrhosis of the liver following malaria is not impossible. Thus there was no obvious relation in

Case C between the enormous increase in round cells in the portal spaces and the focal necroses or the capillary thrombosis. Nor was there any evidence that the round cells were being converted into fibrous tissue. Still these collections were quite like those which one sees in fresh nodules of cirrhosis of the liver. Dock has observed a similar extensive perivascular portal infiltration in a very acute case of malaria in a young man.

V.

CASE D.—*Double tertian malarial infection, associated with general streptococcus infection; symptoms of an acute nephritis with general anasarca manifested during life. Remarks on the bacterial infections and protozoan invasions which may be concurrent with malaria.*

Abstract of clinical record. (Prof. Osler.)

L. W., aet. 23, oysterman, married, admitted January 9th, 1892, complaining of shortness of breath with general dropsy. Family history unimportant. Patient has been previously healthy; denies syphilis; gonorrhoea nine years ago. Has never used alcohol in excess. Some three months before entrance, his work required him to stand in cold water daily for about two weeks. At the end of this time he noticed that his feet and body began to swell, that his urine was scanty and high-colored, sometimes even bloody, and that frequently he had to rise two or three times during the night to urinate. Somewhat later he observed that he was becoming short of breath, especially on exertion. Three weeks before admission he had a severe shaking chill, the first during his illness, and for the next two weeks he had chills nearly every day. During the past week, he states that he has had no chills. The dropsy has gradually increased, and the dyspnoea has become progressively more intense. Of late the urine has not been bloody, and the amount, he thinks, is larger than formerly.

Temperature on admission, 97.8°. Pulse under 100. Anasarca general. Patient rather dull and stupid. Pilocarpine $\frac{1}{6}$ gr. hypodermically repeated once caused profuse sweating.

Note dictated October 1, 1892.—"Medium sized man of good musculature; lips and mucous membranes a little pale; tongue coated; face much swollen; feet and legs oedematous. Abdomen a good deal distended. Respirations, 24; pulse, 84.

Thorax.—Percussion, resonance good in front; deficient behind at right base where vocal fremitus is absent and the respiration is distant. On auscultation the sounds are clear in front; behind and in the axillæ numerous fine râles are audible. Heart sounds clear at apex and base.

Liver dulness merges almost directly into colon tympany at the 7th rib. Splenic dulness begins at the 8th rib. Though uniformly distended the abdomen is tympanitic and no movable dulness can be obtained.

Urine.—Dark in color, 1000 cc. in amount. Sp. gr., 1017; albumen abundant; many hyaline, darkly granular and epithelial casts present."

This case was looked upon clinically as one of acute nephritis. The existence and character of the fever were noted as unusual.

Dr. Osler, in commenting on the case in clinic, alluded to the existence of the fever, the mode of onset, and to the occurrence of chills, and stated that the existence of malaria was negatived by the absence of plasmodia from the blood. Unfortunately, through a misunderstanding among the assistants, each believing that the other had looked for the parasites, no examination of the blood had been made.

By January 23rd, the patient had become more oedematous. The pulse was 140; fluid was now demonstrable in the right pleural sac and in the peritoneal cavity. The urine still contained large quantities of albumen and casts. The fever persisted and was rather remittent in type ranging between 99° and 104° F. Hot baths, diluents and diuretics were given.

On the 24th and 25th the patient was much worse, took nourishment badly; the respirations were rapid and the pulse was feeble. The general anasarca became extreme and there was marked conjunctival oedema. The heart sounds remained clear throughout the whole course of the disease. Death occurred on the 26th of January, seventeen days after admission.

Autopsy. (Dr. Councilman.)

Anatomical Diagnosis.—Acute malarial fever; general streptococcus infection; subacute Bright's disease; malarial pigmentation of organs; chronic passive congestion; general anasarca; infarctions of kidneys; erysipelas.

Body of strongly built light mulatto; face and neck markedly oedematous; livor mortis in dependent parts; general subcutaneous oedema; scrotum markedly swollen. On the left shoulder, and on the inner aspect of both thighs there are blebs containing clear straw-colored liquid surrounded by areas of reddish discoloration.

The peritoneal cavity contains about one litre of straw-colored fluid, which contains large soft clots. The pleural cavities also contain a considerable amount of serous fluid.

Heart of medium size, chambers contain fluid blood and soft clots; weight, 300 grams; myocardium dark reddish-brown in color; all valves normal. Aorta abnormally small and thin, measuring in circumference, just above valves, 4.5 cm.; at middle of thoracic aorta, 4 cm.; at diaphragm, 4 cm.; at bifurcation, 2.75 cm. The common iliac vessels measure 2 cm. in circumference; the left subclavian, 1.9 cm.; the innominate, 2.5 cm. Pulmonary artery normal.

The Lungs.—The surfaces of both are smooth, and both are crepitant throughout. The consistence is increased, color dark red, moderate coal-pigmentation.

The Liver.—Weight, 1600 grams; dimensions, 25 x 16 x 8 cm.; Surface smooth; exquisite outlining of lymphatic network on surface. Consistence about normal. Color on section dark chocolate-brown color. Lobules visible.

The Spleen is small, weighs only 100 grams; size, 12 x 7 x 3 cm.; capsule smooth, not much thickened; consistence very firm. On section the substance is almost black, of a much darker tint than the liver. The Malpighian bodies are not visible. The trabeculae are visible and apparently increased in thickness.

The Kidneys together weigh 400 grams. They are both alike in size and general appearance. On the surface of each a few small fresh infarctions with hemorrhagic margins are visible. The capsules strip off easily. The general color of the external surfaces of the kidneys beneath the capsules is yellowish-brown, marked by scattered opaque darker areas, and here and there by minute hemorrhages. The whole kidney has a rather soft oedematous feel. On section the cortex has a yellowish appearance and is rather translucent; pyramids reddened, contrasting sharply with the lighter colored cortex. On some parts of the cortex the striae are well marked, in others they are less apparent or invisible. Average width of cortex 1 cm. A small amount of fluid exudes from the cortical substance on pressure. The glomeruli are indistinct. The pancreas is oedematous. The adrenal glands are normal in size but it is noticeable that they are darker in color than normal.

The stomach is moderately dilated; both it and the intestines contain an excess of mucus. The intestines are generally distended and their walls are oedematous.

The bone-marrow is intensely pigmented, reddish-brown in color. The brain is small, especially in the frontal regions; weight, 940 grams. The pia is firmly adherent. No marked pigmentation. No hemorrhages or focal disease.

The Blood.—Examined fresh from the peripheral veins and various internal organs showed enormous numbers of malarial parasites, most of them nearly full grown, others only half grown (tertian type), many of them enclosed within the protoplasm of large mononuclear leucocytes. No flagella seen.

Frozen Sections of the kidney show a very little fat in fine droplets in the glomeruli. The epithelial cells of the tubules in the labyrinth are much swollen and are filled with fine albuminous granules and hyaline droplets.

Many of the tubules are dilated and are lined by low epithelium. Casts are numerous in sections and in urine collected from the bladder. Coagulated albumen is visible in the capsular spaces, in frozen sections made from bits of kidney previously fixed in boiling water. The capsular epithelium is swollen and evidently proliferated.

Bacteriological Examination. (Dr. Flexner.)

Cover slips from the heart's blood prepared and stained in the ordinary way showed numerous chains of streptococci.

Cultures.—At the autopsy, the surface of the organs was burned with a hot knife, punctured through the burned area, and tubes of agar-agar were inoculated from the internal tissues. Esmarch roll-tubes were employed; after being kept in the thermostat for twenty-four hours at 37° C they were examined with the following results: The tube from the lung was found to be closely crowded with extremely minute colonies of streptococci, no other micro-organisms being present. The heart's blood, kidney, liver, bone-marrow and spleen all yielded many colonies of streptococci, here also in pure cultures. The tube from the spleen contained many more colonies than that from the liver.

The tube inoculated from the bile contained a few—about one dozen—colonies of streptococci. Tubes were also inoculated from the fluid in the erysipelatous blebs and from the oedematous subcutaneous tissue at their margins. In those from the latter a pure culture of streptococci was obtained.

Microscopical Examination.—The Liver.—In sections examined with very low powers (8 to 16 diameters), it is easy to make out dilatations of the central and sublobular veins and of the capillaries about the central veins, and also that the large amounts of dark malarial pigment which are present are rather peculiarly distributed. Instead of being most abundant, as is ordinarily the case, according to those who have examined large numbers of malarial livers, at the periphery of the lobules, in this instance the pigment is situated in more or less well-marked zones which correspond nearly to the outer limits of the areas of dilated capillaries. Small amounts of pigment press into the areas of capillary dilatation, and some pigment can be seen in the parts of the lobules in which the capillaries are not dilated, but the great bulk of the pigment is certainly present in the zones described. The portions of the lobules nearest the central veins, and those nearest the peripheries are comparatively free from malarial pigment.

On examination with higher powers, the black and brownish-black malarial pigment is seen to be chiefly included by large makrophagic cells within the liver capillaries, and it is to the accumulation of these cells in the zone previously described, that the peculiar distribution of the pigment as seen with very low powers must be attributed. These large cells in which by far the greater portion of the malarial pigment is contained, vary considerably in size shape and general appearance. The smallest ones correspond in size to the ordinary mononuclear leucocytes, the largest reach the size of giant cells, and are equal in bulk to three four or more times that of the smaller ones. Between these two limits there are many intermediate sizes. Many of the cells have round smooth margins, others are polyhedral, many are oval or ovate in shape. These cells usually contain a single round, or more often an oval vesicular nucleus; sometimes two vesicular nuclei are present. The protoplasm of these cells, when not too much obscured by included substances, can be seen to take a feeble stain in haematoxylin and often to contain larger and smaller vacuole-like spaces, some of which may represent fat droplets. But as a rule the protoplasm is scarcely visible, owing to the presence of the large accumulations of extraneous substances and structures which have been included within it. It was somewhat puzzling at first to decide as to the exact nature of the different contents of these cells. In thick sections the protoplasm appears to be filled simply with coarse irregular masses of black and blackish-brown malarial pigment, but in thin sections and by various modifications in the staining technique it is possible to distinguish easily a number of different morphological elements. In the largest cells, the protoplasm of which is crowded with black pigment, it can be made out that most of the pigment does not exist in irregular blocks (although some apparently does), but in definite, more or less regularly spherical masses. Often there is an appearance as though a malarial organism, which has been included, had suffered rupture of its capsule, allowing the partial escape of the pigment. From the shrunken malarial capsules (in which the pigment exists usually as a more or less fused and homogeneous mass, rather than as distinct granules as seen in the well preserved organisms) delicate dotted lines of minute pigment particles can be seen running in different directions out into the protoplasm of the phagocytes. Occasionally in these very large cells, much more often in the smaller ones, well developed spherical tertian malarial organisms, with pigment granules arranged in lines in their peripheries and central non-pigmented areas can be seen. The number of included organisms and shrunken capsules (cadavers, corpses, or débris of malarial organisms), is often large. As many as twenty and even thirty were counted in some cells, and doubtless a number of the very large cells, where the bodies lie closely crowded in different planes so that they can be counted only with great difficulty, contain even greater numbers of them. Dark brownish-black pigment in little clumps, resembling that seen near the centers of segmenting tertian organisms, is also observed within these cells, and part of the irregular masses of malarial pigment may represent aggregations of this segmental pigment.

Included in many of these large cells are visible red blood corpuscles, sometimes only one or two, sometimes large numbers of them—true red blood-corpuscle-carrying cells. There are also numerous irregular yellow particles and masses which look like fragments of red corpuscles. On (or in) some of the corpuscles granules of malarial pigment are seen infected red blood corpuscles (?). In specimens hardened in alcohol, stained with alum-cochineal, and treated with a fresh solution of ferrocyanide of potassium to which a little pure hydrochloric acid had been added, very instructive views of the contents of these makrophages are obtainable. Many of the yellow particles and masses give very definitely the blue haemosiderin reaction, and in this way a much better idea of the number of partially destroyed red blood corpuscles present can be gained. The fully formed intraphagocytic red corpuscles do not as a rule give the haemosiderin reaction, but retain their yellowish tint; some of them indeed are distinctly brassy in appearance, although these brassy corpuscles are by no means so numerous in the liver of this case as in that from a case of an aestivo-autumnal infection. Occasionally, a red disc of full size and normal shape will give the distinct Berlin blue reaction, and at times particles of malarial pigment can be seen lying on such a blue disc. A great many of the fragments of corpuscles do not yield the blue color with the ferrocyanide mixture, so that in the large cells yellow corpuscles, yellow fragments, blue corpuscles and blue fragments lie mixed in varying proportions, along with altered and unaltered malarial parasites and malarial pigment.

As might be expected in cells whose protoplasm is burdened with such large amounts of deutoplasm, the position and shape of the nucleus often deviate widely from the normal. Nearly always placed excentrically, the nucleus is sometimes pushed to the extreme margin or end of the cell, and instead of exhibiting its ordinary oval contour it may assume a stellate or more often a crescentic outline. Sometimes indeed the nucleus is seen to be fragmented, or to be absent altogether, and in such cells the protoplasm has a swollen glassy appearance and is much more refractive than normal.

Besides the malarial organisms and their remains, blood corpuscles and their derivatives, many of these edacious cells contain within their protoplasm still other objects. Thus it is not uncommon to see inside them one or more white blood cells. These included white corpuscles usually have nuclei of the lymphoid type, sometimes they have polymorphous nuclei; or again the two kinds may be present together lying alongside one another in the protoplasm of the same including cell. Sometimes these incorporated white cells contain within their protoplasm well preserved malarial organisms or free pigment. Their nuclei as a rule stain sharply, and their protoplasm does not appear to be abnormal. At other times the protoplasm of the included cells is more highly refractive than normal, and has a clear glassy look; the nuclei may be fragmented and stain intensely, or they may be entirely necrotic and refuse to take up any of the ordinary nuclear dyes. When the large cell is necrosed (hyaline protoplasm, fragmented or non-staining nucleus) and contains within it white blood corpuscles, these are likely to be leucocytes with polymorphous nuclei.

Finally in the protoplasm of the makrophages (the case being one of general streptococcus infection) cocci occur singly, in chains, or in groups of chains; sometimes the streptococci lie within the protoplasm of included white blood corpuscles.

The makrophages above described lie usually close to the walls of the capillaries but do not appear to have any organic connection with the walls. Sometimes a single one is large enough to practically close the lumen of a capillary. They appear, too, to be lodged quite frequently at the junction of capillaries and to cause obstruction to the flow of blood.

There is an astonishingly large number of well preserved tertian malarial organisms, nearly fully developed, present in the liver. A comparatively small proportion of these apparently uninjured organisms are free in the blood or enclosed simply in red blood corpuscles. The majority of those in the blood-vessels are enclosed within the protoplasm of the large mononuclear leucocytes, from one to six in a cell, and a few within the protoplasm of leucocytes with polymorphous nuclei; although in these latter one rarely sees more than one or two in a cell. As has already been mentioned, a few well preserved malarial parasites are found among the contents of the free makrophages, and as will be pointed out later, occasionally uninjured parasites at the same stage of development as those in the blood are discernible inside the endothelial cells lining the hepatic capillaries. All these organisms appear to be of the same size and present very much the same appearances. They are nearly full grown and ready for segmentation; indeed two definite segmenting bodies (central pigment surrounded by minute oval hyaline bodies) were seen in the blood in one section of the liver. The malarial organisms in alcohol sections in this case studied carefully with the best apparatus are seen to be tolerably regular spheres, consisting of a thin peripheral layer in which all the pigment is included, and a central more or less spherical mass which does not contain pigment. The brownish-black pigment is not always irregularly distributed in the outer layer, but in favorable specimens it can be seen to have a definite arrangement in lines, with clear spaces between, running like meridians at certain intervals in the directions of the poles. Even in the organisms with ruptured capsules this arrangement can sometimes be made out. The central or usually slightly excentric spherical non-pigmented area stains in certain basic dyes, often quite intensely in methylene blue, only feebly and often not at all in haematoxylin and in aqueous magenta (vide Spleen Plate). The outer layer of the organism in which the lines of pigment run takes no tint with these dyes. The pigment in some organisms tends to accumulate toward one pole, and to retract from the other. This morphology of the organism can best be made out in the larger veins, where the plasmodia are very numerous. The free organisms and infected red blood corpuscles, like the leucocytes, have a tendency to collect along the walls of the veins, where in this case (there being a leucocytosis of considerable degree), together with the leucocytes large phagocytic cells and chains of streptococci, they form masses of considerable size clinging to the venous walls. In some of the veins, however, leucocytes and organisms are fairly evenly distributed among the red corpuscles throughout the lumina of the vessels. Some of the capillaries and smaller veins are crowded with cells malarial parasites and streptococci. The leucocytes (mono- and polynuclear) scarcely ever contain the shrunken remains of the parasites, but besides the well preserved forms there is seen in them an occasional ruptured organism, segmental pigment, and sometimes streptococci. Here and there the nucleus of a white corpuscle is fragmented, and a mononuclear leucocyte may be seen enclosing within its protoplasm a lymphocyte or a leucocyte with a polymorphous nucleus.

The spindle-shaped endothelial cells lining the small veins, and especially those of the hepatic capillaries, present interesting appearances. Many of them contain small fragments of straw-colored blood pigment, and in the protoplasm of some of them malarial pigment, malarial organisms, and the remains of parasites are included. Sometimes streptococci are to be seen within the endothelial cells. The extraneous matter in the endothelial cells does not as a rule greatly increase their bulk, being arranged more or less regularly at the poles of the nuclei, but now and then endothelial cells are met with which are much swollen, contain large masses of pigment and parasitic remains, and almost obliterate the lumen of the capillary. Occasionally lymphoid cells or polynuclear leucocytes are seen within them. Some of the endothelial cells have hyaline protoplasm similar to that described as occurring in the necrotic makrophages.

In the sections stained with alum cochineal which were afterwards treated with the acid ferrocyanide solution and examined with a low power, the walls of the capillaries (more marked in some regions than in others) are seen to be outlined by delicate blue pigment. Examination with higher powers shows this to be haemosiderin within the protoplasm of the capillary endothelium. Not all of the particles of straw-colored pigment, however, in these cells yield the haemosiderin reaction; while in some of the cells they are all turned blue, in others they all remain yellow, and again cells are seen with blue and yellow particles mixed in varying proportions.

The spaces between the capillary walls and the liver cells are generally exaggerated, more especially towards the centers of the lobules. The cells in these spaces (Kupffer's cells) have acted as phagocytes; they are swollen and exhibit contents analogous to those which characterized the intra-capillary makrophages. The swelling of these cells in some places has been so great as to press the adjacent capillary wall markedly out into the capillary lumen. The rows of liver cells, more especially those about the central vein, are atrophied and are narrow. The cells contain an excess of yellow-brown pigment; the nuclei are more numerous than normal, are shrunken and stain intensely in nuclear dyes. There are very few actual necrotic liver cells to be seen, but now and then one is visible containing a fragmented nucleus, or a nucleus which does not stain at all. The protoplasm of these cells is hyaline and may be invaded by leucocytes with polymorphous nuclei. The liver cells do not contain malarial organisms or pigment. Much of the yellowish-brown pigment within the rows of liver cells yields a blue reaction with Perl's test. In some areas the actual ectasis and liver cell atrophy is extreme. In those where the changes in the liver cells are the same the capillaries appear to be collapsed and the number of nuclei present is striking. The liver cells of the peripheries of the lobule are large and some of them contain giant nuclei. In the connective tissue of the portal spaces there are some large cells filled with clumps of dark malarial pigment. There is a slight increase in the number of lymphoid cells in these spaces.

Spleen.—The comparatively small size of the spleen is due to the existence of chronic interstitial changes. On microscopic examination the capsule and trabeculae generally are found to be much thickened, and there is thickening and fibrous transformation of the reticulum of the pulp. The spleen, however, also shows evidences of less chronic lesions. The spleen-pulp is hyperaemic and there is a marked increase in the number of colorless cells in the pulp-cords and within the splenic veins and capillaries. A goodly number of red blood-corpuscle-carrying cells can be made out. While some of these cells contain only red blood corpuscles as inclusions, in others are also seen malarial parasites and pigment together with some nucleated white cells.

There are large numbers of malarial parasites in the large and small splenic blood-vessels, exactly similar to those described in the liver. Some are free in the blood, or lie on or in infected red corpuscles; the majority of well preserved organisms are contained within the protoplasm of cells; there are from one to six in each of the cells, which are of the size and general appearance of large mononuclear leucocytes. As a rule the nuclei of these cells stain well, but occasionally they do not take the dyes at all. A few well preserved organisms and some free brownish-black (segmental?) pigment are to be seen within the leucocytes with polymorphous nuclei. The nuclei of a few of the mononuclear and polynuclear leucocytes in the splenic capillaries are fragmented, the chromatin being broken up into deeply staining masses of varying sizes.

In addition to these cells there are in the splenic capillaries, veins and pulp, many makrophages, large usually mononuclear cells, whose swollen protoplasm is crowded with masses of malarial pigment, the shrunken remains of malarial organisms, organisms with ruptured capsules, and occasionally with one or several well preserved organisms in the same stage of development as those free in the blood. These cells contain in addition many red blood corpuscles and fragments of red corpuscles, part of which yield the haemosiderin reaction. On some of the included red corpuscles particles of fine malarial pigment are visible, suggesting that these corpuscles when received into the phagocyte were infected with malarial parasites. These makrophages may contain, like those in the liver, white cells, and some of these included cells may contain other cells, so that one sees cell within cell within cell, and as the protoplasm of all three may contain extraneous substances, one may speak of phagocyte within phagocyte within phagocyte. The nuclei and protoplasm of including and included cells vary in appearance—sometimes the former, sometimes the latter show evidences of degeneration or necrosis. Streptococci are very abundant throughout the spleen; they appear in single chains and in masses of chains. They are especially well defined in the sections stained with methylene blue and eosin, and in those prepared according to Weigert's method for the differentiation of fibrin, bacteria and hyaline. They can often be seen enclosed within the protoplasm of cells, mononuclear and polynuclear leucocytes, intravascular makrophages, and endothelial cells. Some of the small veins and splenic capillaries are actually thrombosed with masses of streptococci, white corpuscles, malarial organisms and phagocytes, matted together with filaments of fibrin.

The endothelial cells in the spleen, like those of the liver, are swollen and contain within their protoplasm blood pigment, part of which has been transformed into haemosiderin. A few of them also contain malarial organisms, cadavers of parasites, and free fine and coarse malarial pigment; streptococci may be seen within some of them.

A certain number of the large makrophages within the splenic pulp are arranged in groups, and present a peculiar appearance. The cells are much swollen, and besides the ordinary contents of collapsed organisms etc., large areas of the swollen protoplasm show yellowish-brown pigment arranged in dotted lines ramifying through the protoplasm, which is often hyaline, so that we have something which looks like tangled masses of pigment lines, often over-lying and hiding the nucleus from view, and enclosing minute areas of hyaline protoplasm within the felt-work (*vide* Plate VI). These lines of pigment often appear to run out from the pigment masses enclosed within the cells. The pigment in these lines when in focus is seen to be dark brownish-yellow in color, while that out of focus may be of a pale straw color. The malpighian corpuscles of the spleen are somewhat swollen and are almost entirely free from coarse malarial pigment. On close examination, however, fine malarial pigment, yellowish-brown in color, arranged often in lines, and not enclosed within cells, can be made out in many of the malpighian bodies lying in the interspaces between the lymphoid cells.

The Kidney.—An examination of many glomeruli shows considerable variation in the size of the capsular spaces. While in some instances the glomerulus almost completely fills out Bowman's capsule, the space being a mere chink, in others the latter is equal in size to one-third of the whole capsule. The space is not always empty but may contain coagulated albumin, red blood corpuscles and shadows, or a few mononuclear cells (desquamated epithelium). The fibrous capsules are not thickened except occasionally where an atrophied glomerulus is visible. Frequently just outside the capsule of Bowman a narrow clear space can be made out, and this may contain a few cells, chiefly polynuclear leucocytes, or even be crowded with them. In many of the capsules the capsular epithelium is evidently proliferated, the whole inside of the space being lined by nuclei with intensely staining chromatin. The glomerular capillaries vary in their size and contents; some of them are empty, others are distended. Occasionally one is seen to be plugged with streptococci. The number of white corpuscles within the glomerular capillaries also varies; they are very irregularly distributed; in some glomeruli scarcely any are present; in others one two or more of the glomerular capillaries may be packed full of polynuclear leucocytes. In a section stained in methylene blue, a capillary is visible plugged at one point with streptococci and crowded throughout the rest of its extent with leucocytes with polymorphous nuclei,—reminding one forcibly of the appearance of the capillary glass tubes in an experiment in positive chemotaxis. On the other hand masses of cocci may be seen with no neighboring leucocytic accumulation. The nuclei of the polynuclear leucocytes vary in appearance; some stain sharply and take on the ordinary forms; others stain less sharply, have a blurred look and assume bizarre shapes. The protoplasm of the polynuclear leucocytes frequently contains granules or minute clumps of granules of malarial pigment, occasionally a well-formed parasite or short chains of cocci. There is some malarial pigment in the glomeruli contained within the protoplasm of mononuclear cells. The majority of the malarial parasites in the glomerular capillaries are outside nucleated cells.

Here and there in specimens stained with aqueous magenta a giant spindle-shaped nucleus is visible.

The lumina of the convoluted tubules are for the most part wide and are lined with rather low cubical epithelium. There are a few areas of dilated tubules, in which the lining epithelium is flattened so as to resemble endothelium. The nuclei of the epithelial cells as a rule stain normally, although in some swollen cells they stain feebly, and in some tubules the nuclei are shrunken and the chromatin stains more intensely than normally.

Many of the convoluted tubules and collecting tubules contain hyaline casts; and hyaline droplets are visible within the swollen lining epithelial cells. These droplets, both the finer and the coarser, and the upper portions of the hyaline casts stain intensely in Weigert's fibrin stain. Occasionally desquamated epithelial cells and a few red blood corpuscles and round yellowish striped urinary concrements are to be seen within the lumina of the tubes.

The intertubular capillaries contain enormous numbers of streptococci (methylene-blue, Weigert's fibrin stain). Many of them are dilated and completely plugged with cocci, and sometimes chains of cocci are visible in narrow pericapillary spaces. As in the glomerular vessels, some of the intertubular capillaries are crowded with leucocytes. Some of the small veins in the cortex are actually thrombosed with masses of streptococci, large numbers of malarial parasites, white corpuscles (some of which are necrotic), and pigment clumps. No bacteria other than streptococci are present anywhere in the kidney.

In the interstitial tissue of the kidney there is a slight but evident increase in the number of cells of the lymphoid type. There are small nodal masses of smaller and larger round cells, usually with but little perinuclear protoplasm, many of them with fragmented nuclei. These minute nodes may contain, besides lymphoid cells, single polynuclear leucocytes or epithelioid cells.

Sections of the kidney treated with ferrocyanide of potassium and hydrochloric acid show an almost entire absence of cells containing haemosiderin. Here and there, however, a little is visible within the protoplasm of the endothelium of the vessels.

The infarcted areas of the kidney present the lesions ordinarily seen under these circumstances—anaemic necrosis and neighboring reaction. The whole of the necrotic area—glomeruli, tubules, blood-vessels, interstitial tissue—refuses to stain in the ordinary nuclear dyes, and has an increased affinity for eosin. The only nuclei which stain are those of polynuclear leucocytes which have invaded the interstitial tissue everywhere, and are accumulated in large numbers at the margins of the infarcted areas, and in the neighboring dilated blood-vessels. There is extensive nuclear fragmentation in these polynuclear leucocytes, and the most varied distortion-processes (abschnürungsvorgänge) of their nuclei are visible. Many of the blood-vessels at the apices and in the peripheries of these infarctions are thrombosed with streptococci, enormous numbers of malarial organisms, over 100 of which were counted inside the lumen of one vessel, and white cells. Small bits of the kidney hardened in Flemming's stronger solution and stained with aqueous magenta yield very instructive sections. Fine fat droplets are visible in the glomeruli and in the epithelium lining the capsular spaces. The convoluted tubules are not extensively fatty; some are entirely free from fat droplets, others show numerous smaller and larger droplets, especially at the proximal ends of the lining epithelial cells. Fine fat droplets are also visible in the protoplasm of some of the leucocytes in the vessels, and also in the smooth muscle fibres of the arteries. The desquamated epithelial cells within the lumina of the tubules contain numerous rather coarse fat droplets. The cells of the convoluted tubules in sections prepared in this way are seen to be finely granular and the hyaline degeneration of the protoplasm is well shown. Many of them contain large vacuole-like spaces which sometimes displace the nuclei. In some of the tubes free red blood corpuscles, polynuclear leucocytes, and malarial organisms are visible. The last named are sometimes free or lie on red blood corpuscles, sometimes they are enclosed within cells. They are to be seen in both polynuclear and mononuclear cells within the lumina of the convoluted tubules. In one tubule, besides numerous red blood corpuscles and shadows, four free well-formed malarial organisms and a mononuclear cell containing within its protoplasm five malarial organisms of the same stage of development can be made out. Pictures such as these were seen too often to be accounted for by technical accidents. Occasionally red corpuscles malarial parasites and white cells are visible within the glomerular capsular spaces.

The Bone Marrow.—The malarial parasites in the marrow are for the most part enclosed within mononuclear cells; numerous makrophages are here present with contents very similar to those described for these cells in the spleen. Streptococci are numerous, some free in blood-vessels others enclosed within white cells. The endothelial cells contain blood pigment at the poles of the nuclei—part of which yields the blue reaction. There is an increase in the number of the white cells in the marrow, and a considerable number of nuclei are fragmented. Nucleated red blood corpuscles are abundant, as are also degenerated red corpuscles, occurring singly and in clumps. Some of the streptococci in sections treated with ferrocyanide of potassium and hydrochloric acid yield a sharp blue reaction, so that the chains of cocci look as though stained in methylene blue. The same result was obtained with some of the cocci in the spleen.

The Adrenal Glands.—In the literature, the lesions of the suprarenal capsules in malaria have not received the attention which the findings in this case would show that they deserve. The arteries and veins of the capsule are wide and contain many malarial organisms as well as single chains and masses of streptococci; the lumina of some of the veins are completely filled with accumulated leucocytes (mononuclear and polynuclear), malarial parasites in and outside of red corpuscles and streptococci. A few makrophages are also present in the veins of the capsule. There are irregular areas of vascular dilatation throughout the sections. The vessels of the zona glomerulosa are generally distended, as are those of the medulla; in the zona fasciculata and in the zona reticularis the capillary and venous dilatation occurs in areas. It will be remembered that in the liver the rows of liver cells had undergone an extent of atrophy corresponding to that of the capillary dilatation; similarly here in the area of capillary ectasis the adrenal cells are small.

Malarial parasites are numerous in all the distended vessels; many of them are obviously within red corpuscles, a large number are enclosed within the protoplasm of mononuclear leucocytes—from one to four in a cell. Polynuclear leucocytes are numerous; they often contain segmental pigment and occasionally a malarial organism. The makrophages, with contents like those in the liver and spleen, are present in considerable numbers in the adrenal capillaries, being somewhat irregularly distributed through the cortex and medulla; they are perhaps most abundant in the outer portion of the zona fasciculata, and fewest in the zona glomerulosa which is tolerably free from pigment masses when looked at with very low powers (8 and 16 diameters). The endothelial cells are phagocytic here as in the liver, their nuclei are large and vesicular, their protoplasmic contents quite similar to those of the intra-capillary makrophages, except that they consist rather more of blood pigment and less of malarial pigment, the foreign substances being arranged mainly at the poles of the nuclei. Outside the capillary walls, between them and the adrenal cells of the zona fasciculata, here and there mononuclear makrophages are visible, not unlike the phagocytic cells of Kupffer in the liver. It is possible to make out, too, that a few of the true adrenal cells in places contain within them malarial pigment and infected corpuscles—a fact which should not surprise us when we consider the close relation of certain parts of the adrenal parenchyma to the veins which has been recently demonstrated by Manasse.

In places there are capillary thrombi of pure streptococci, and cocci in single chains or in clumps are irregularly distributed in the capillary districts. Here and there in sections stained in methylene blue they are visible inside of cells (leucocytes, makrophages, endothelium of capillaries).

Many of the adrenal cells, often in foci, are swollen, vacuolated, and fatty, and show fragmented nuclei. The chromatolytic changes are best seen in sections stained in aqueous magenta.

The Lungs.—The pulmonary and pleural veins are widely distended, and in them enormous numbers of malarial organisms are visible. The parasites are chiefly in red blood corpuscles, but many of them have been included, often along with streptococci, by white cells (chiefly mononuclear, but also polynuclear). The white corpuscles tend to accumulate in groups, and they, together with infected red corpuscles, makrophages, free malarial parasites, and masses of streptococci, are frequently massed near the walls of the vessels. The parasites are present, too, in considerable numbers in the pulmonary capillaries and in branches of the pulmonary artery. Lesions associated with coal pigmentation, and moderate emphysema are present, otherwise the lungs show no marked alterations. No other tissues from this case were preserved for microscopic examination.

The fact that the malarial infection was not recognized during life, the enormous number of parasites, the extensive phagocytic processes, and particularly the mixed infection and the lesions in the kidneys make this case one of more than ordinary interest.

It may not be out of place here to make a few general remarks concerning the bacterial infections and protozoan invasions which may be concurrent with malaria.

In the clinical section of this fasciculus (Report by Thayer and Hewetson) the occurrence of multiple malarial infections is considered, and the fact that an individual may be infected at the same time with different groups or generations of the same organism or of organisms of different types, is found to account for many of the manifold manifestations of the disease which may be met with. But in addition to a knowledge of such multiple *malarial* infections, a consideration of the possibility of the co-existence with malaria of other protozoan infections, and of certain bacterial diseases, both local and general, throws some light upon certain problems connected with malaria which have been heretofore obscure.

Concerning protozoan infections concurrent with malaria little is known. In the Johns Hopkins Hospital one case of malaria has been met with in which there was an associated dysentery due to the amoeba coli.

The bacterial infections which may be associated with malaria are numerous. In the first place the occurrence of a complicating pneumonia in malaria, which led years ago to so much polemical literature, is now satisfactorily explained. The pneumonias which were believed to be due to a malarial poison are now known to be due not to this cause, but to an associated bacterial infection. Manson and others have described forms of pneumonia peculiar to the disease when occurring in conjunction with malaria, and it was believed that this pneumonia was particularly prone to terminate fatally. The review of the whole subject by W. T. Howard in 1859 had an important influence, and still merits careful reading. Osler opposed the view that the pneumonia in malaria was special to the latter disease. Finally Bignami, Marchiafava and Guarnieri have described cases which came to autopsy, at which careful bacteriological examinations were made, by which it was proved that the croupous pneumonias of malaria, like other cases of croupous pneumonia, are due to infection with the micrococcus lanceolatus.

In addition to croupous pneumonia, bronchitis and broncho-pneumonia are frequent complications of malaria, and probably may be due to any one of the pyogenic organisms. The much disputed typho-malarial fever, by the light of our present knowledge, presents no difficulties. It is now well established that the majority of cases of so-called typho-malarial fever and typho-intermittent fever are really genuine cases of typhoid fever. That a typhoid infection may co-exist with an invasion by the malarial parasites is indeed certain; upon this point the cases reported by Osler and by Gilman Thompson have left no room for doubt.

The rare cases in which an acute ulcerative endocarditis is seen in conjunction with malaria, now that the etiology of the endocarditides is better understood, will probably turn out to be examples of mixed bacterial and malarial infection.

Erysipelas sometimes co-exists with malaria; at least one such case has been met with in the wards of this hospital.

Of the predisposition to dysentery depending upon alterations in the nutrition of the mucous membrane lining the alimentary canal we have already spoken. The chances of bacterial ingress and the possibilities of a general septic infection in such cases is obvious. Cases of general streptococcus infection, such as the one described under the head of Case D, are undoubtedly rare.

VI.

ON THE UNEQUAL DISTRIBUTION OF THE PARASITES IN THE BODY IN MALARIAL INFECTION.

The recognition of the existence of pigment in the blood and in the various internal organs of patients suffering from malarial infection antedated by many years the discovery of the organisms of malaria by Laveran in 1880. But the studies of these earlier observers went beyond the recognition of its mere existence, since it was noted by quite a number of them that the pigment was not equally distributed throughout the body. Thus, in the well known case of Meckel in an insane patient, in whom the spleen was enlarged and deeply pigmented, particles of pigment were found in various parts of the body, and it was suggested that these had been swept out of the spleen by the blood and carried by the current to the other organs.

Virchow in 1848, in describing the melanaemia of a malarial patient, speaks of the large accumulation of pigment in the spleen and liver, and at the same time notes the finding of this substance enclosed in the cells in the blood of the heart.

Planer suggested that the comatose and apoplectic forms of severe malaria might be explained by the lodgment of emboli of pigment in the brain capillaries. Frerichs attributed the atrophy of the parenchyma of the liver, observed in some of the cases, to obstruction in the liver capillaries.

Since the discovery of the malarial parasite, those who have had opportunities of studying specimens of the fresh blood from a large number of cases of malarial infection, have not only been able to recognize certain distinct types of parasites as belonging to the various clinical forms of the disease, but have also been able to add some curious facts relative to the distribution of the organisms in the blood and organs. Councilman, Celli and Marchiafava and others observed in cases of the comatose form of pernicious malaria, the frequent occurrence in the brain of capillaries plugged with parasites. Councilman, too, early pointed out that the number of crescentic forms of the organism in the circulating blood was seldom large, but that their tendency was to accumulate in considerable numbers in the spleen.

The question of the unequal distribution of the parasites in the body assumes especial importance when considered in connection with the three main types of the malarial organisms. Without entering into a detailed description of the individual observations which have led up to our knowledge of the subject as it may at present be formulated, the broad statement may be made that in infections with quartan parasites one sees the most equal distribution of the parasites throughout the blood and various organs, and that in infections with parasites of the aestivo-autumnal variety the most unequal distribution is encountered. In infection with parasites of the tertian type, the character of the distribution may be said to stand between that of the quartan and that of the aestivo-autumnal infections, approaching perhaps a little more closely to the former.

In the quartan fevers the parasites are nearly always to be seen in numbers in the blood in any of the peripheral parts, and during the paroxysm many segmenting bodies, although they show a decided tendency to accumulate in the organs, are observable in the blood taken from the finger-tip or from the lobule of the ear. Indeed, so regular is the distribution of the organisms throughout the body in this type of malarial fever, that a tolerably definite estimate of the severity of the infection can be made simply from the number of organisms to be seen in the fresh blood slide.

The parasites in tertian fever, although usually quite abundant in the circulating blood, show decidedly a more marked tendency to accumulate in the internal organs, such as the spleen, the liver, and the marrow of the bones. This is notably true at the time of the paroxysms when the segmenting organisms, although usually still present in severe infections in considerable numbers in the peripheral blood, are for the most part retained in the internal organs and especially in the spleen.

But it is in the infections with the aestivo-autumnal parasites, infections which include the majority of comatose and other pernicious cases, that the most curious and marked variations in the distribution of the parasites are to be met with, and the findings in these cases have gone far to make clear the diverse and startling clinical manifestations to which these infections may give rise. It is in these cases more particularly that pathologists, through observations at post-mortem examinations, have been able to make important contributions to the understanding of a disease, the main progress in which is undoubtedly due to the work of the clinical investigators.

In the aestivo-autumnal infections, the number of organisms in the blood circulating in the peripheral parts afford as a rule very insufficient data upon which to base an idea of the severity of the infection. As clinical experience has taught, numerous slides prepared from the peripheral blood may show very few organisms, and these often of the type most difficult to recognize, while in a drop of blood taken from the spleen quite a large number of the parasites may often be made out with ease.

The occurrence of segmenting organisms in the peripheral blood is a phenomenon of extreme rarity in aestivo-autumnal infections.

Golgi, Bignami and others have pointed out the fact, which can easily be substantiated by careful observation, that in aestivo-autumnal malaria the distribution of the parasites may vary in different parts of the same organ. Thus in the fluid obtained from tapping the spleen in different regions, the number of organisms is prone to vary considerably, and in sections of the spleen, liver, and other organs, it is not difficult to convince one's self of the disparity in the number of organisms in different vascular territories.

Among the most interesting and most important of the local accumulations of the parasites is the formation of parasitic thrombi. In the comatose forms of malarial fever it is not uncommon to find capillaries and small veins in the brain distended with masses of malarial parasites of the aestivo-autumnal variety, which probably are identical with the so-called pigment thrombi of the early observers. These may be pigmented organisms and segmenting forms, or according to Bignami, the thrombi may sometimes be made up of the small pale non-pigmented bodies first described by Marchiafava and Celli.

The profound disturbances of nutrition necessarily consequent upon such a condition, which is not unfrequently accompanied by necrosis, would alone, without a consideration of the effects of the toxines which the parasites produce, suffice to explain many of the clinical phenomena referable to intra-cranial involvement.

It is not to be supposed that in any given case, all the capillaries are alike affected. As a matter of fact, while two or three may be completely filled with parasites, their neighbors for some distance around may be almost or entirely free from them. When we consider the many variations possible in the implication of the capillaries in any organ, the diversity of the disturbances of the cerebral functions observable clinically becomes easily understandable. It is not difficult to conceive that herein may lie the key to the transitory aphasias, the variation in degree extent or duration of the paralyses, or of the mental irregularities occasionally noticeable in the severer forms of aestivo-autumnal fever; and when, along with other things, we remember that comparatively limited disturbances of the circulation in certain of the vital centres, such as the medulla,[1] suffice at times to cause sudden death, it is not surprising that the type of malarial infection which is associated with the possible occurrence of the capillary thrombi of parasites should have won for itself the title of *malaria perniciosa*.

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[1] Marchiafava has recorded a case in which he noticed a special localization of the parasites in the neighborhood of the bulbar nuclei.

In describing the findings in Case B, attention was directed to the accumulations of parasites within the capillaries and small veins of the mucous membrane of the stomach, and to the necroses on the surface of the mucosa, which could fairly be attributed to the disturbances in the nutrition of the part. There are numerous instances in the literature in which, after death, a similar condition has been found in the vessels of the mucous membrane of the intestines, the patient during life having shown the symptoms of profound intestinal disturbance and even of an acute dysentery. The cases are so characteristic as to be worthy of a definite place in nosology and the names *malaria perniciosa cholerica*, and *malaria perniciosa algida* have been suggested to describe these forms.

It would probably be fair, arguing by analogy, to assume—and many observations would seem to confirm the view—that the occurrence of similar parasitic thrombi in other organs of the body may lead to alterations in nutrition and function which materially influence the course and progress of the disease.

Any attempt to explain the reasons for this unequal distribution is beset with many difficulties. While the slow circulation and the calibre of the vessels in certain organs certainly play a part, yet the distribution of parasites in all forms of malaria is, as we have seen, very different from that of inert substances when introduced into the circulating blood. Undoubtedly, many factors have to be considered, and how far any one or more are concerned in a given case is difficult to determine.

In another section, in which phagocytosis is dealt with, the localization of the parasites in certain organs inside of cells will be more fully commented upon. As Bignami suggests, the activity or inactivity of the phagocytes of a certain organ may have an important influence upon the distribution. He lays stress, too, upon the fact that the parasites are usually endoglobular, and that infected red corpuscles, from loss of elasticity or other physical alteration, may be impeded in their progress and tend to accumulate in the viscera in which the circulation is slowed. It is certainly true that in the abdominal area where the slowness of the circulation is accentuated in malaria, owing to obstruction in the liver by endothelial swelling or accumulation of makrophages within the capillaries, the massing of the parasites is ordinarily marked, while in organs in which the circulation is most active, very few parasites as a rule are present. That the parasites and infected red cells collect along with the white corpuscles on the inner walls of the larger veins is a fact which could be confirmed in many of the specimens from the autopsies of this report, but as to the explanation of this phenomenon nothing is as yet certainly known.

As regards the tendency in the pernicious cases to the formation of thrombi composed of parasites in certain vascular territories our knowledge is most at fault. The idea that certain capillaries become plugged with makrophages, and that in the dilated vessel behind the point of obstruction the corpuscles in the stagnant blood all become infected, will not suffice for the explanation of all the instances. That vaso-motor influences in certain vascular areas play, as Bignami suggests, an important rôle seems plausible, especially in cases of the pernicious algid form.

It is perhaps not impossible to learn something from the analogies observable in tumor metastases, in bacterial infections or even in simple intoxications. It has long been a puzzle to pathologists why in cases of general sarcomatosis or carcinosis, where the distribution is through the general circulating blood, that in some cases one organ or set of organs, in other cases other portions of the viscera have remained free or nearly free from metastatic growths.

Again as regards the general bacterial infections those who have as a matter of routine made bacteriological investigations of all the organs at a number of autopsies, will be familiar with the fact that in such cases the bacteria even at perfectly fresh autopsies are by no means equally apportioned through the blood and viscera. Indeed, it is a common occurrence to find that one or two of the organs contain relatively many fewer bacteria than the others. But that there is little regularity in the inequality of distribution is shown by the study of numerous cases of general infection with the same micro-organism, *e. g.* the streptococcus. Whereas the plate cultures made from the spleen in one case of septicaemia may be closely crowded with colonies and those from the liver contain only a few, in another instance the conditions may be exactly the reverse. Every one is acquainted with the relative immunity of some organs in acute general miliary tuberculosis, an immunity which can be made out often from the naked eye appearances alone, although it is often difficult to decide whether the irregularity is an expression of a primary inequality of distribution, or to differences in the resistance offered to the local multiplication of the distributed organisms or again to the different effect which they produce on the tissues in which they develop.

And after all when we consider the fact that in malaria we have to deal with a crude mixture of malarial parasites, blood corpuscles and blood plasma, the anomalous distribution of the parasites, as ascertained by post-mortem examinations, should be much less difficult to account for than the unequal diffusion through the organs of substances which are dissolved in the blood, a phenomenon which of late has attracted considerable attention. It is scarcely necessary to call to mind that normally certain chemical bodies are removed from the circulating fluid by various glands to serve in the manufacture of secretions. Again, the discovery of the accumulation of poisons in certain organs, *e. g.*, morphine in the liver, spleen and bone marrow, and certain other vegetable poisons in the liver, for purposes of elimination or neutralization must be reckoned among the observations which help to make general toxicology interesting. In the domain of bacterial toxicology, Welch and Flexner have demonstrated the occurrence of definite focal lesions in the tissues of the body produced by a soluble poison circulating in the blood, a finding which is scarcely compatible with any assumption other than that the dissolved poisons are not evenly distributed even in the individual organs.

Now that the vital characteristics and varying sensibilities of unicellular organisms are becoming better known and appreciated, we have learned to have more respect for a cell as an individual, and the conclusion that this unequal distribution is dependent upon a complexity of factors will not excite surprise. If it be borne in mind that the parasites are constantly exercising their metabolic functions; if the question of food relations and that of the influence of excretory substances from the parasites together with the alterations in the metabolism of the cells of the various tissues (*e. g.*, those dependent upon the destruction of red corpuscles) be taken into account, it will be seen that the whole problem of anomalous distribution, as influenced by factors incident to the parasite and factors incident to the cells, may become extremely complicated, and that we can scarcely hope in the very near future that all the intricacies, whether they be due simply to mechanical factors or to those which we must regard as the outcome of vital influences, will be explained.

VII.

ON PHAGOCYTOSIS IN MALARIA.

Among those who have insisted upon the importance of the part played in malaria by the so-called phagocytes are Metschnikoff, Guarnieri, Bignami, Laveran, Dock, and especially Golgi and Bastianelli. As has been said above, a study of the literature shows that malarial pigment had been observed in the cells of the different organs and in the white cells floating in the blood long before the parasitic nature of the disease had been established, and a great deal of this pigment is now known to be within the bodies of the parasites.

The inclusion of the malarial pigment and of the malarial parasites within white cells, fixed or floating, occurs in all cases of malaria, although the extent of the process varies somewhat in different individuals, and with the different varieties of malarial infection. The microscopic examination of the cases which came to autopsy here, showed that the reports of other observers on this subject had not been exaggerated.

The cells actively concerned in phagocytosis are not all of one kind. Besides different varieties of leucocytes, certain of the fixed cells of the organs, the endothelial cells generally, but especially those in the liver and spleen, the cells of Kuppfer in the former, and the cells of the pulp-cords in the latter, take no unimportant part in the process.

The contents of these different phagocytic cells vary also. Speaking generally, it may be stated that the cells concerned may enclose within their bodies any of the following: (1) red blood corpuscles, many of them altered, others apparently little changed; (2) fragments of red corpuscles; (3) masses of haemosiderin (probably formed within the cells); (4) malarial parasites, in different phases of the developmental cycle, many of them endoglobular, many of them degenerated or going to pieces; (5) malarial pigment, especially the central pigment clumps from segmenting parasites; and (6) white cells both mononuclear and polynuclear. A phagocytic cell is sometimes seen to contain all of these structures at one time, but this is not a common observation. Special names have been assigned to the phagocytic cells in accordance with the character of their contents—thus the leucocytes containing malarial pigment are spoken of as "pigmentiferous" or "melaniferous;" the cells containing red corpuscles as "globuliferous;" while those containing parasites are known as "amoebiferous" cells. Following this nomenclature the cells containing other phagocytes might be called "phagocytiferous," just as those containing white corpuscles have been spoken of as "leucocytiferous," but it is doubtful if much is to be gained by any extension of this awkward terminology.

The different forms of phagocytes seen in our cases have been fully described in the protocols of the microscopic examinations, and need not be further considered here. One point to which attention may perhaps be directed is the manifest division of labor which exists among the various forms of phagocytic cells. While any one of the varieties seemed capable of taking up at times almost any of the substances above mentioned, yet when the tissues are studied carefully it is easy to make out that they do not all contain these various substances in the same proportions, but that as a matter of fact the white corpuscles and endothelial cells appear to possess more or less definite elective affinities. For example, in Case D while the mononuclear leucocytes contained the majority of well preserved parasites, the polynuclear leucocytes showed a preponderance of the segmental pigment; while the makrophages in the spleen and liver contained large numbers of infected and otherwise altered red corpuscles and remains of malarial parasites, the endothelial cells of the spleen and liver often contained blood pigment to the exclusion of all other visible kinds of foreign material. Laveran, Councilman, and Golgi early noted that leucocytes carrying pigment were most abundant in the blood just after the onset of a paroxysm, and suggested that the increased number of pigmented corpuscles might depend upon the setting free of large quantities of pigment during segmentation. Supposing that there might exist a periodicity to the phagocytosis corresponding more or less nearly to the developmental cycle of the parasite, Golgi made certain studies, the result of which convinced him that the idea had a basis in fact. From these investigations he concluded that the white cells in the organs, particularly in the spleen, played even a more active part in phagocytosis than those in the blood, a conclusion which had also been reached by Metschnikoff from the study of sections of the spleen and liver in malaria. Bastianelli found further in his extensive study of the leucocytes in malaria a marked increase in the number of pigmented leucocytes in certain cases at the beginning of the febrile paroxysm, but as might have been expected saw less evidence of periodicity in the aestivo-autumnal cases. He seems inclined to attribute the major share of the phagocytic work to the large mononuclear elements. The same writer confirmed the observations of Bignami concerning the degeneration of phagocytic leucocytes and suggests that the diminution in the number of leucocytes in malaria may be attributed to this cause. John S. Billings, Jr., who made accurate counts of the total number of leucocytes, and also differential counts of the various forms of white corpuscles by Ehrlich's methods of color analysis, before, during and after the paroxysms, found that in certain cases there was always a diminution in the number of leucocytes during the febrile paroxysm. In a chart accompanying his article in which a composite curve of the temperature is compared with a similar one representing the number of white corpuscles, it is evident that, while just before the chill the number of white cells to the cubic millimetre is approximately normal, there is a steady though not very marked increase in the number for from two to three hours until a maximum is reached, after which there is a relatively sharp and steady decline corresponding with the fall in temperature until a minimum is reached which is considerably below the normal. As to the color analysis of the leucocytes, Bastianelli found a decrease in the leucocytes with polymorphous nuclei with an increase in the large and small mononuclear elements. According to Billings a decrease in the polynuclear and an increase in the large mononuclear cells is constant, while there is no regularity as to the percentage of small mononuclears and eosinophiles.

The clinical observations just referred to are of considerable interest in connection with the appearances in the organs at autopsy, and it is interesting too to compare the examples of phagocytosis observable in the blood drawn from the circulation during life (*vide* a report by Thayer and Hewetson) with those seen in the sections from the cases now reported. According to these observers it is extremely rare to notice any active phagocytic tendencies on the part of the mononuclear elements to parasites in blood taken from the finger or ear, although it is by no means uncommon to see a leucocyte with a polymorphous nucleus gradually enclose a flagellating parasite or a fragmented extra-cellular body in the fresh blood slide. It will have been seen above, however, that in the blood in the sections from Case D the majority of parasites are enclosed within large mononuclear leucocytes. It has been stated, too, that neither the parasites nor the including cells necessarily show evidences of degeneration. The question naturally arises, "Could the enclosing of the parasites by the large mononuclear leucocytes in this case have been a post-mortem phenomenon?" Dock has shown that the malarial parasites are arrested in their development soon after the death of the patient, and it is of course quite conceivable, though in my opinion it is improbable, that certain changes occurring in the parasites inside the body after death rendered them suitable to be taken up by the large white cells. It is unfortunate that in this case no blood examination was made during life. So many of the large mononuclear leucocytes as seen in the sections contain parasites within their protoplasm, that had the ingestion occurred ante-mortem it could scarcely have been overlooked upon examination of the fresh blood.

The original statement of Metschnikoff that the endothelial cells of the capillaries, especially in the liver, take up the parasites has been questioned by some observers. The tissues from the autopsies here reported unquestionably confirm Metschnikoff's statement, though as we have said, the endothelial cells are much more prone to take up the remains of altered blood corpuscles than to include malarial pigment or the parasites.

The red blood-corpuscle-carrying cells and the huge phagocytic cells of the spleen attract special attention. When one studies sections of the spleen and sees the enormous number of these makrophages, the accumulations of fragmented red corpuscles, the necroses, and the dilatation of the blood-vessels in this organ, he has not to go far to seek an explanation for its enlargement in malarial infection. The number of makrophages which are carried from the spleen through the splenic vein into the liver cannot fail to be of considerable significance. As was pointed out in the description of the tissues they frequently appear to occlude the liver capillaries, and to offer a serious impediment to the onflow of blood. Guarnieri thought that this obstruction in the liver capillaries might account, in part at least, for the enlargement of the spleen (venous stasis), and suggested that possibly the pernicious forms of malaria might depend upon an intoxication due to the disturbance of the functions of the liver—a view which he has doubtless given up long before now.

The question may fairly be asked, "What becomes of these migrated spleen cells loaded down with ingested material?" If we can judge by an examination of the tissues elsewhere, there are comparatively few carried through the liver into the general circulation, unless indeed the greater number of them have been diminished in size, and have gotten rid of some of their contents so that they were able to pass through. This they could do in part through cellular digestion. It seems to me, however, that, carrying as they do, besides malarial parasites and malarial pigment, considerable quantities of haemoglobin and of blood coloring matter already altered within the cell so as to give the blue iron reaction, these cells may exercise an important function in carrying to the liver the materials for the manufacture of bile. It is not inconceivable that these makrophages lying in direct contact with the endothelium of the hepatic capillaries could yield up a portion or all of their contents to the latter. It would indeed be interesting if it should turn out that the blood pigment in the makrophages, in the vascular endothelium, and in Kupffer's cells stood in some such direct relation to the bile manufactured by the liver cells. Certainly the liver cells must draw their iron substances from the blood, and from what we know now-a-days of the varied capacities of white blood corpuscles and of endothelial cells, the occurrence of some such interchange of raw materials as has been hinted at would not be surprising. It may be that the study of pathological accentuation of the bile-making activities of the liver may throw light in the future on the still obscure physiological processes which go on in this organ.[1] The metabolic processes of the body tend towards economy; the re-making of materials by different organs is common, the refuse from one organ often being essential for the nutrition and well being of certain of the others (law of Treviranus); and this being so, the relations of phagocytosis to the nutritional activities of the body form an interesting topic for investigation.

The makrophages in the vessels of the mucous membrane of the alimentary tract have been mentioned in connection with Case A. Dock describes finding one similar cell in one of his cases. It is generally stated that eosinophilic cells never act as phagocytes in malaria. The late Dr. Oppenheimer, however, recently showed me in a slide of fresh blood a makrophage which contained large, round, yellowish, refractive granules which closely resembled the ordinary eosinophilic granulation; the cell enclosed several infected corpuscles.

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[1] Compare the researches of Dr. William Hunter, *On the Physiology and Pathology of Blood Destruction*, Brit. Med. Jour., 1892, ii, p. 1159 and 1223.

It is not improbable that the active process of phagocytosis, aside from the mechanical obstruction which the cells may cause, helps to determine the irregular distribution of the parasites in the body. At any rate it is certain that the parasites tend to accumulate in ordinary cases in the spleen and liver, the sites where the phagocytosis is most active. We have already pointed out, however, that the phagocytosis can be only one of many factors which influence the distribution.

There is a considerable amount of literature bearing upon the relation of phagocytosis to "natural resistance" and to "spontaneous cure" in malaria. It is a perfectly well ascertained fact that many patients suffering from malaria do, when placed under more favorable hygienic conditions, get entirely well without the administration of quinine or of any other drug. It is by no means uncommon to see patients begin to improve almost immediately after being put to bed in a hospital ward, the paroxysms becoming successively less severe, and the organisms gradually disappearing from the blood until all have vanished. What the natural mechanisms of defense are which lead to spontaneous cure, and which inhibit the growth and multiplication of many parasites even in the severer infections, it is as yet impossible to say definitely. All authorities are agreed that many of the progeny of segmenting organisms are disposed of at the end of each paroxysm, since did all the young ones gain entrance to red corpuscles and go on to full development, the blood would after a very few paroxysms show very few uninfected red globules, and those who hold that the blood serum kills off many of the small hyaline forms before they gain entrance to the interior of red corpuscles are not without grounds for their belief. Others maintain that the white corpuscles, the endothelial cells, and the spleen-pulp cells enclose many of the segments immediately, even before they have been deleteriously affected by the blood serum. The relative efficiency of the blood serum and of the phagocytes with relation to natural resistance, is being fought out on this as well as on other grounds. There can be little doubt (*vide* protocols) that many of the parasites taken up by the phagocytic cells are enclosed within red corpuscles, and it may very well be that the alteration in the bodies of the red corpuscles may help to determine, especially in the spleen, their inclusion by white cells. That the rereception of the parasites can do harm to the cells in many cases would seem to be evidenced by the fact that many of the makrophages are necrotic, their nuclei staining feebly or not at all in basic dyes, and their protoplasm showing an increased affinity for acid dyes like eosin. The diminution in the number of leucocytes after a paroxysm, however, is much more probably due to the effects of toxines set free at segmentation, and if so would be quite analogous to the similar diminution (leukolysis) which immediately follows the experimental injection of bacterial toxines into animals.

The changes which the parasites undergo within the bodies of the white cells are interesting to watch. It would appear that sometimes the parasite ruptures and that the pigment is gradually set free to be distributed in more or less regular lines throughout the protoplasm of the including cell. How long the parasites may live after inclusion appears doubtful. That they are taken up while alive seems certain from the many observations of skilled investigators. It is usually taken for granted that the phagocyte is the active agent and takes up the parasites, a much more likely view than that the parasites enter the white cells to feed on their deuteroplasm (fragmented or degenerated red corpuscles). It is not certain, however, that the parasites may not continue an intra-phagocytic existence at least for some time, especially if the protoplasm of the phagocyte is degenerated. Golgi has even gone so far as to suggest that the parasites may grow and multiply within certain of the body cells. Bignami cannot conceive of any explanation for the so-called "cases of latent infection" in malaria, that is, those instances in which an apparently cured malarial infection subsequently becomes active, without the patient having in the meantime been exposed to re-infection in a malarial district, except by assuming the continuance of some resistant forms inside of cells. Bignami argues that inasmuch as certain cells, leucocytes and endothelial cells for example, are known to take into themselves a certain number of sporulating forms, and further, since in patients with a recently cured malarial infection who have died from some intercurrent disease certain cells in the spleen, liver and bone marrow, retain the traces of infection, it is much more likely that the germs of latent infection remain stored up in these cells than that they should exist for such a length of time free in the circulation. For if the parasite is capable of assuming some persistent form (crescentic or otherwise),[1] it is scarcely likely that such a form could long be retained inactive in the intercellular fluids, since it would almost certainly be taken up by phagocytes. Bastianelli and Bignami, however, combat Golgi's idea of the intra-cellular development of the parasites. There are many examples of latent bacterial infections, and the resistance of certain bacterial forms to the intra-cellular digestion is generally appreciated (cf. the researches of Wyssokowitch, Metschnikoff, *et al.*). For the present, however, it must be granted that we do not fully understand all the conditions which underlie latent infection.

Among the more interesting of the observations on phagocytosis in malaria are those dealing with the inclusion of certain phagocytes by other phagocytes—sometimes of phagocyte by phagocyte even to the third degree. As has been stated, the including cell sometimes looks necrotic, while in other instances it is the included cell which shows degenerative changes; occasionally both cells yield normal staining reactions. That such inclusions are not infrequent the sections from the fatal cases described in this report indisputably prove. Any attempt at explanation must be speculative. We can conceive of active small cells being attracted to the degenerating protoplasm of a large cell. This might explain the instances where the including cell looked degenerated. Or we can imagine the makrophage taking into its substance an enfeebled small phagocyte, in which case the included cell will be degenerated. Finally we can conceive of a small active phagocyte being attracted to a large, more sluggish phagocyte by the masses of food stuff (broken down red corpuscles, etc.) contained within the latter. A consideration at the present time of such cannibalistic and thieving tendencies on the part of the white cells would lead us too far afield, but such studies are among the many attractive problems connected with the sociology of cells, which, it is to be hoped, the physiologists will work out in the near future.

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[1] As Bignami points out, it is evident that some explanation other than the resistance of crescents is necessary to account for the obstinacy of certain tertian and quartan infections.

DESCRIPTION OF PLATES.

PLATE III.

CASE C.—Liver—showing an accumulation of small round mononuclear cells in a portal space.

PLATE IV.

CASE C.—Liver—stained with haematoxylin and eosin—showing an area of necrosis with accumulation of leucocytes, many of which have distorted nuclei. Fine particles of malarial pigment may be seen within the endothelial cells of the capillaries and within some of the leucocytes.

Near the lower angle of the drawing a small thrombus containing numerous leucocytes is visible.

PLATE V.

CASE C.—Liver; haematoxylin and eosin; high power.

Fig. 1.—Hyaline thrombosis of an hepatic capillary; accumulation of leucocytes; nuclear distortion; a little malarial pigment present.

Fig. 2.—Thrombosis of adjacent capillaries; disappearance of intervening liver cells; leucocytic accumulation; distortion and fragmentation of nuclei.

PLATE VI.

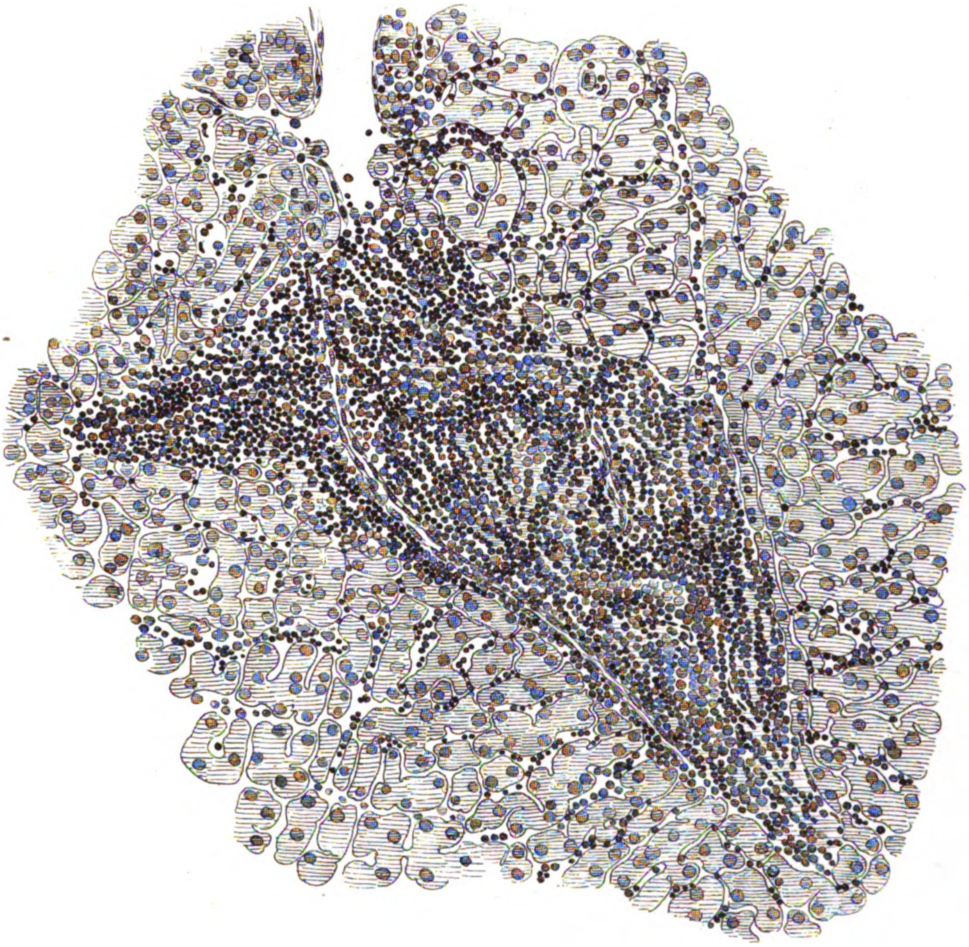
CASE D.—Spleen in mixed malarial and streptococcus infection. Tissue hardened in alcohol; section stained in methylene blue; accumulation of parasites and cocci within the vessels. Many of the malarial parasites have been absorbed by phagocytes. In the lower angle of the large vessel to the right a large mononuclear leucocyte is visible which contains four parasites. Occasionally cocci and malarial parasites are to be seen inside the same phagocyte.

The makrophages in the splenic pulp, some containing coarse clumps, others finer particles of malarial pigment, are numerous.

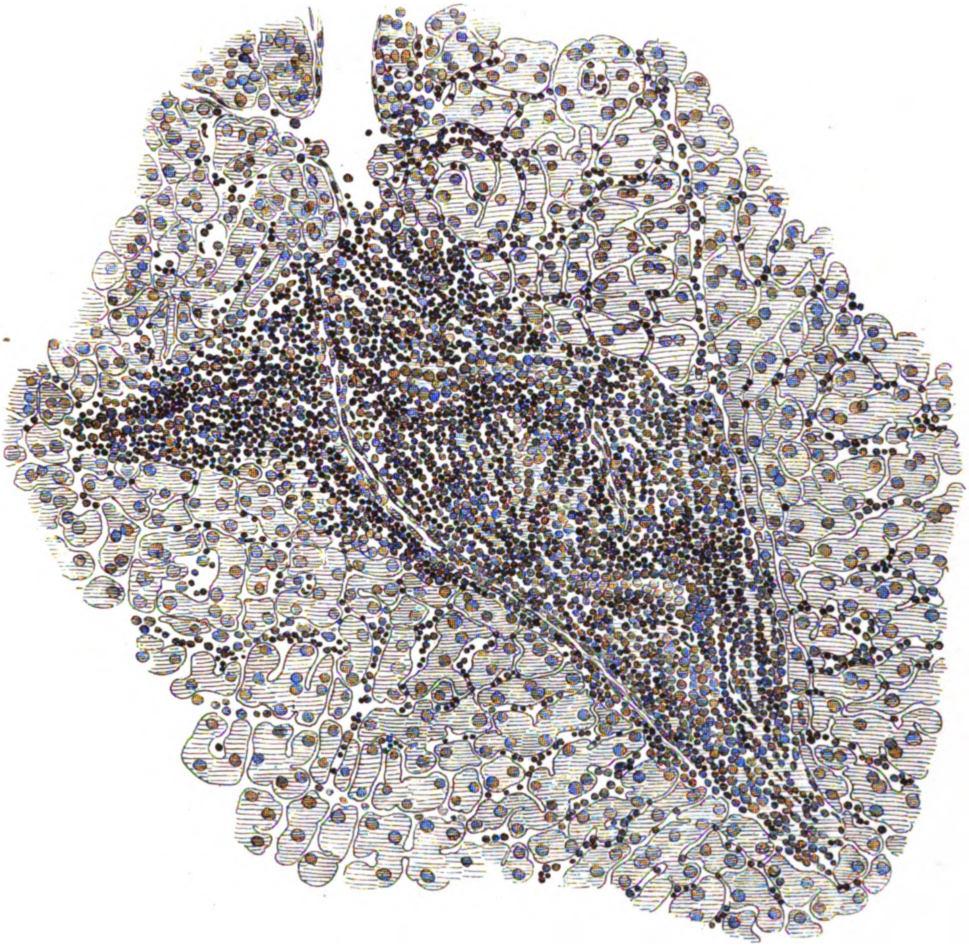
Inside the vessels the makrophages are quite like those described within the hepatic capillaries of this case.

Some of the endothelial cells contain malarial pigment within their protoplasm.

A blue-stained non-pigmented sphere within the malarial parasite is well shown in several parts of the drawing.



Max Brödel. fec. Lith Anst v E A Funke, Leipzig



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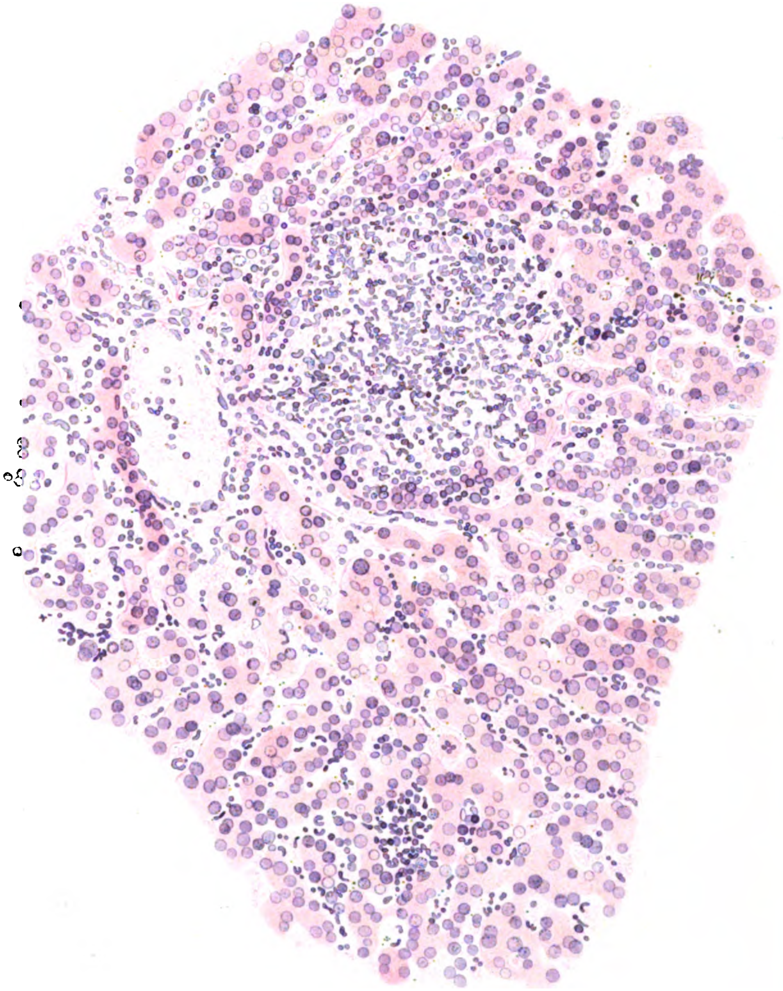

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Fig. 1.

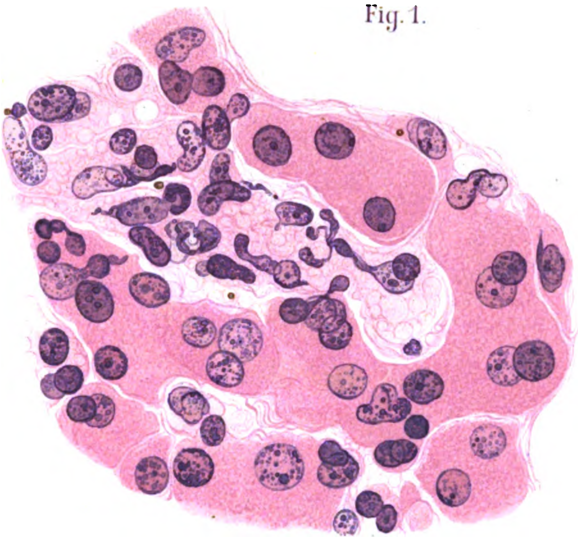
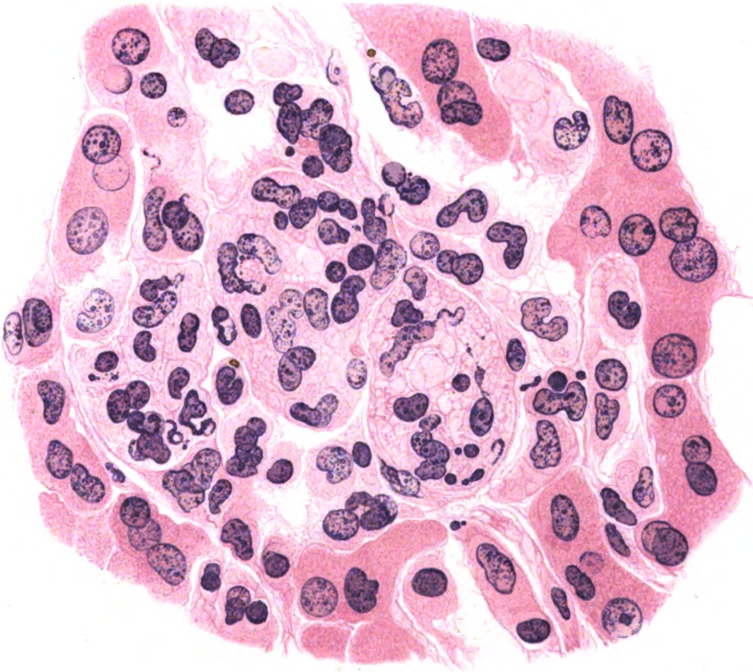


Fig. 2.



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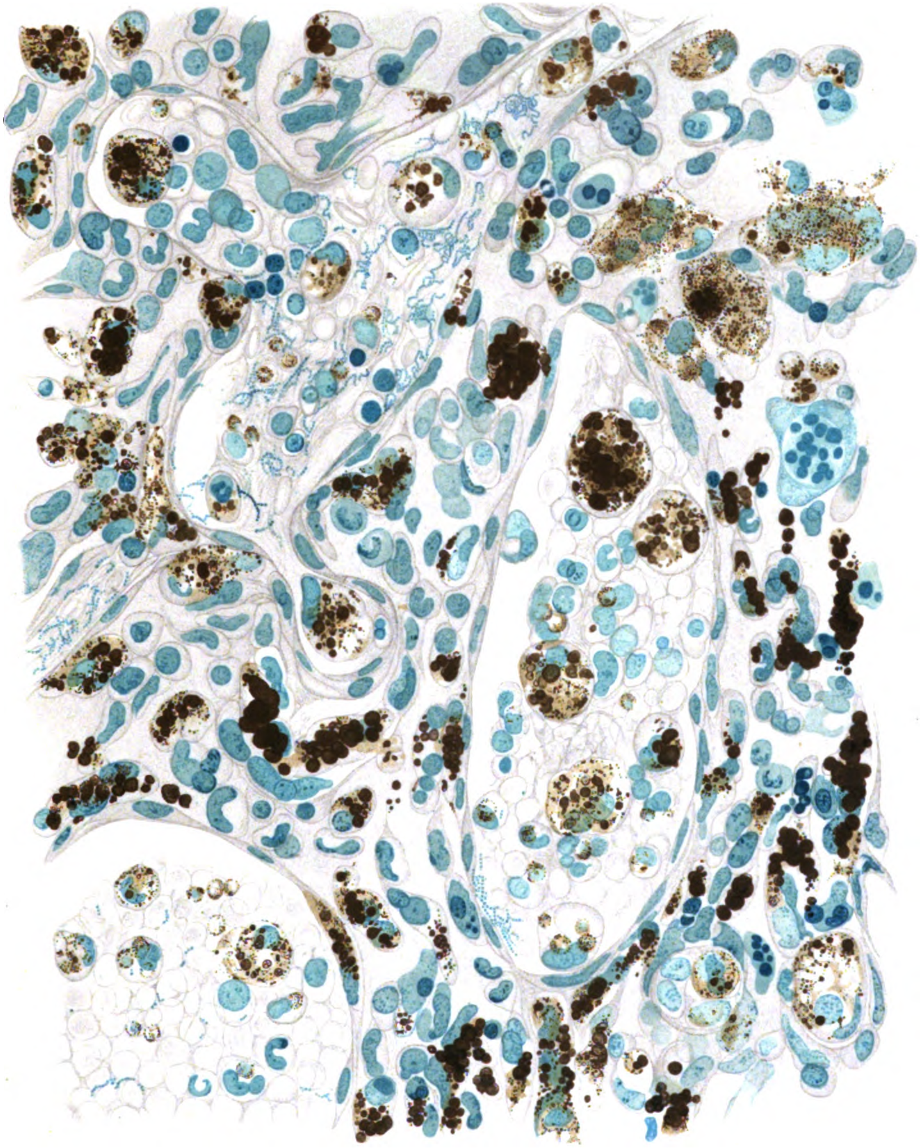

M. Brodel fec. Lith. Anst. v. E. A. Funke Leipzig.

I.—ANALYSIS AND SUMMARY OF THE CASES.

BY WILLIAM OSLER, M. D.

In Volume IV of the *Reports* (1894) we dealt with 229 cases of typhoid fever under treatment in the Medical Department for the first four years of the Hospital work. We here deal with 160 cases treated to conclusion during the 5th and 6th years, ending May 15th, 1895.

SEX.—124 were males, 36 females.

For the six years.—311 were males and 78 females.

RACE.—147 were white, 13 were colored.

For the six years.—355 white, 34 colored. The ratio of colored to white in the admissions to the wards is about 1 : 7.

NATIONALITY.—Americans (exclusive of colored), 77; Germans, 44; Poles, 8; Irish, 7; English, 5; Scandinavian, 4; Russian, 3; Bohemian, 3; Welsh, 1.

For the six years.—Americans, 154; Germans, 114; Irish, 25; English, 15; Scotch, 2; Welsh, 1; Scandinavian, 12; Poles, 12; Bohemians, 12; Russian, 3; Italian, 1; Syrian, 1; Finn, 1.

AGE.—Five to fifteen, 9; fifteen to twenty, 22; twenty to thirty, 94; thirty to forty, 23; forty to fifty, 6; fifty to sixty, 4; sixty to seventy, 2.

For the six years.—Five to fifteen, 32; fifteen to twenty, 73; twenty to thirty, 203; thirty to forty, 52; forty to fifty, 16; fifty to sixty, 8; sixty to seventy, 5. More than one-half of the cases occurred between the twentieth and thirtieth years.

SEASON.—The admissions in each month were as follows:—

January, 7; February, 4; March, 2; April, 9; May, 1; June, 5; July, 20; August, 34; September, 31; October, 25; November, 18; December, 3.

For the six years.—January, 16; February, 9; March, 5; April, 14; May, 9; June, 14; July, 42; August, 74; September, 69; October, 65; November, 52; December, 19.

LOCALITY.—*For the six years.*—From the City, 303 cases; from Baltimore county, 50 cases; from Maryland, outside Baltimore county, 14; from outside Maryland, 18; from steamers and doubtful, 4.

MORTALITY.—In the 5th year eighty-one cases were treated, with five deaths—a rate of 6.1. In the 6th year seventy-nine cases were treated, with seven deaths—a rate of 8.8. Of the one hundred and sixty cases considered in this report, twelve died—a rate of 7.5.

For the six years.—Of three hundred and eighty-nine cases treated to May 15th, 1895, thirty-four died—a mortality of 8.7 per cent.

For the five years since the introduction of the Brand method, three hundred and fifty-six cases have been admitted, of which twenty-six have died—a mortality of 7.03 per cent.

Of 299 bathed cases, 20 died—a mortality of 6.6 per cent.

II.—SPECIAL FEATURES, SYMPTOMS AND COMPLICATIONS.

BY WILLIAM OSLER, M. D.

I.—ANALYSIS OF THE GENERAL SYMPTOMS.

I.—The Rash.—Rose-spots were noted in 119 cases.
Total for the six years.—318, 81.7 per cent.

PECULIARITIES OF THE RASH.—(*a*). *Hæmorrhagic.*

James M., aged 22 (Hosp. No. 7728). On admission the rash was profuse on the abdomen and back, and was petechial in the groins. The eruption was abundant throughout. The attack was of moderate severity. Recovery.

G. F., aged 21 (Hosp. No. 9321). The attack was severe.

March 4th, '94.—"Rash is copious on abdomen and back. Just below the right clavicle there are several ecchymotic spots, and there is an area the size of a silver dollar into which superficial hæmorrhage has taken place. In this region nine or ten older ecchymotic rose-spots are seen."

March 7th.—"Spots are well marked on the neck and as high as the angle of the jaws; there are none on the face; they are very abundant on the arms. The spots described on the 4th have become more hæmorrhagic, and a similar large area has developed below the left costal border in the mid-axillary line. There are scattered petechiæ also upon the posterior axillary folds."

Michael S., aged 22 (Hosp. No. 11392). The attack was severe, with high fever at the outset. On admission the rash was abundant on trunk and arms; two days subsequently the spots in the flanks and groins had become hæmorrhagic. The patient did well.

Michael U., aged 21 (Hosp. No. 11745), admitted January 4th, 1895, on the 6th day of the fever. The attack was severe and persistent. The rash was profuse upon the trunk, and the spots were particularly numerous on the upper part of the chest. They were present also on the arms and a few were seen on the thighs. On the 10th spots of simple purpura appeared on the skin of the right shoulder and of upper arm. On the 11th many of the rose-spots on the abdomen were hæmorrhagic and did not disappear on pressure.

Jesse T., aged 28 (Hosp. No. 11861), admitted January 19th, 1895. The attack was severe and the fever was high. The eruption was profuse, and on the abdomen the spots became hæmorrhagic.

(*b*). *Rash Persistent while Patient Afebrile.*

John G., aged 21 (Hosp. No. 8461), admitted on 10th day. The temperature was 105°, with unusually abundant rash, of a deep rose-red color. The temperature became normal on the 21st day. On November 3rd, the 23rd day, when the temperature had been normal for 36 hours, fresh spots appeared on the abdomen. On November 6th, the 26th day of illness, there were fresh rose-spots. The rectal temperature had, in a two-hourly record, only registered 99.5° once, and once 100° since 12 midnight on November 1st. On November 9th the spots of the 6th had faded.

Charles S., aged 25 (Hosp. No. 8930). Mild primary attack; severe relapse. Rash abundant. During the 3rd week of the relapse, while the temperature gradually fell from 100° to normal, fresh spots appeared on the abdomen, and on the 23rd day of the relapse, when the morning temperature had been normal for five days, the spots were still visible.

(*c*). *Anomalous Distribution of Rash.*

Augusta A., aged 48 (Hosp. No. 3168), had a very mild attack. The spleen was easily palpable. There were no typical rose-spots on the abdomen, but on the arms and hands there were many slightly raised, red spots looking like those of typhoid fever.

(*d*). *Exceptionally Profuse Rash.*

August G., aged 26 (Hosp. No. 11119), admitted October 11th, 1894, about the end of the 3rd week of the fever. The temperature was high and all the features of the disease well developed. On admission the rash was exceptionally profuse over the entire trunk and on the shoulders and arms, and very thickly set. On the 15th the spots had extended down the arms and forearms; a few were seen on the neck, a number could be seen on the thighs, a few on the legs; none appeared on the face.

(*e*). *Peliomata.*

The only cases were as follows:—

James E., aged 32 (Hosp. No. 3169), admitted the end of the first week. There were well-marked rose-spots, and on the skin of the left flank two steel-gray peliomata.

Carl N., aged 25 (Hosp. No. 9655), had an extensive crop of peliomata which lasted from April 16th, two days after admission, to April 23rd. Pediculi were present on entrance.

The following note by Dr. Hewetson on Peliomata was read at the Hospital Medical Society (*J. H. H. Bulletin,* Vol. V) on the occasion of demonstrating two cases:—

There exists a considerable difference of opinion as to the diagnostic value of these spots. Many writers, particularly the English, believe that they are often seen in the early stages of typhoid fever, and have laid some stress upon their presence, although they admit their occasional occurrence with pediculi. Other observers, especially the French, claim that they do not exist unless pediculi, and more particularly the pediculi pubis, are present; that when the spots exist, the pediculi or their nits can be found if looked for carefully. Our experience leads us to believe that the latter view is correct, as in the cases of typhoid fever in which the peliomata were present, we were able in each instance to find either the pediculi or their nits. There have been several cases, other than typhoid fever, in which these grayish-blue spots were found, but always associated with pediculi. There are at present two cases in the wards, one with catarrhal jaundice and another admitted for chronic bronchitis and emphysema. In neither case is there any elevation of temperature, but in both there are numerous steel-gray spots scattered over the abdomen, thorax, inner sides of thighs, and here and there on the arms and legs. In both the pediculi are numerous, particularly over the pubes, and also in the hair over the various sites where the *taches bleuâtres* are present. In both cases they are quite plentiful in the axillæ, but in neither have they been found on the hairs of the head or face. They do not appear to have caused much irritation; neither patient complained of itching, nor are there marks of much scratching. Indeed, I find that one patient, formerly an Austrian soldier, is quite indignant at the removal of both hair and pediculi. He tells me that they are considered as bringing luck to the bearer, and each sells for from 5 to 10 kreuzers among the soldiers. They had been carefully carried by him for ten years.

Crocker states that "Moursou in 1868 wrote concerning the finger-nail-sized, steel-gray spots of pigmentation (maculæ ceruleæ, taches ombrées) which are frequently seen deep in the epidermis of the affected areas. Duguet in 1880–82 showed that this pigment was contained in the thorax of the animal, opposite the anterior pair of legs, where there are known to be two pairs of salivary glands, and it is probable that the secretion is conveyed into the tissues through the haustellum. Jamieson thinks that the stains have some anæsthetic effect as far as the itching is concerned." In this patient the *taches bleuâtres* stand out plainly against the somewhat jaundiced skin, and, as can be seen, are most numerous in those positions in which the pediculi were most abundant. The pigmentation seems to disappear after the skin containing it has been pinched for a few seconds.

II.—The Fever.—In 119 cases the thermometer registered 104° and over (rectal temperatures). Six cases only had a temperature of 106°. Forty-nine cases had a temperature between 105° and 106°, and sixty-four cases a temperature between 104° and 105°. In no case did the fever reach 107°.

Of the eleven fatal cases during the 5th and 6th years, the highest temperature recorded was 106.3°. Nine had fever above 105°. Case Susie B., given fully on page 345, had a low temperature during the greater part of her stay of 9 days in the Hospital. The highest record was 103.4°, and there were only a few hours in which the temperature was above 103°. In the case of A. B. (p. 468), the temperature was 104° on admission to the ward, but at no time subsequently did it reach the bathing point, 102.5°, except just before death, when it registered 104°.

For the six years.—Of the 389 cases, there were 271 in which the thermometer registered 104° and over. In only one case was the temperature 107°. In 14 cases the temperature was 106°. In 118 cases the register was between 105° and 106°, and in 147 cases the fever was between 104° and 105°.

III.—The Pulse.—There were 56 cases with a pulse rate of 120 and over; in 7 the rate exceeded 130; in 9 the pulse exceeded 140, and in only 2 was it more than 160 per minute.

IV.—Diarrhœa.—In 41 cases the bowels were loose; in 33 cases there were at some time or other during the attack as many as four movements in the day—moderate diarrhœa; in 8 cases there were six or more movements in the day—excessive diarrhœa.

The condition of the bowels in the fatal cases was as follows:—in seven the diarrhœa was moderate, in three excessive, in two the bowels were regular.

For the six years.—The bowels were loose in 117 cases of the 389—30 per cent. In 36 of these the movements were frequent; in 81 moderate or slight.

V.—The Spleen.—In estimating an increase in the volume of the spleen we trust more to palpation than to percussion. With ordinary relaxation of the abdominal walls, the edge of a moderately enlarged organ can be felt during a deep inspiration. With the left hand on the splenic region, the fingers well behind and pressing forwards, the palm pressing towards the right, then the patient is asked to draw a deep breath, and the fingers of the right hand, just below the costal border, will feel the edge of the spleen, which sometimes tilts visibly over them. When the abdominal walls are very resistant, it is better to palpate just as the muscles relax, and to follow the receding wall quickly, when the edge of the spleen may be touched.

In 97 of the 160 cases the edge of the spleen was felt. In two instances in the 6th year the area of dulness was much increased, and yet the border of the organ could not be felt, owing to the tension of the abdominal walls.

For the six years.—In 244 of the 389 cases the border of the spleen was palpable.

2.—RELAPSE.

There were five cases of relapse in the 5th year and nine cases in the 6th—fourteen cases in the one hundred and sixty, *i. e.*, 8.7 per cent. The total number in the three hundred and eighty-nine cases was thirty-two—8.5 per cent. The doubtful cases are not included.

Theresa H., aged 24 (Hosp. No. 8594), admitted November 9th, 1893, at the end of the third week of fever. The temperature fell gradually after fourteen baths, and was normal on the 17th. There was complete apyrexia from the 17th to the 26th—9 days. On the 26th she had meat for the first time. The fever rose that evening to 100.5°, and on the evening of the 27th to 102°. The fever persisted until December 14th—19 days. The range was 102.5° to 104.3°. There were a few spots, but the spleen was not palpable. The tongue was furred. There was no diarrhœa; no complications.

George S., aged 34 (Hosp. No. 8787), admitted September 29th, 1893, on the 14th day of the fever. The attack was severe, and the temperature did not become normal until October 21st. It remained normal until November 2nd—11 days, with the exception of 10 hours of pyrexia on the 24th. On the 2nd he complained of abdominal pains, and there was some distension. The tongue became furred, and the patient felt badly. From the 2nd to the 15th the fever ranged from 99° to 102.5°; the spleen again became palpable, but no definite rose-spots were seen. There was slight diarrhœa. From the 15th to the 19th there were oscillations from normal to 101.5°, and after the 19th the fever did not rise again.

Christopher T., aged 32 (Hosp. No. 8049), admitted August 28th, 1893, on the 22nd day of his illness. The fever was intermittent, and we thought it might possibly be malaria, but the blood was negative. The spleen was easily to be felt, but there were no spots. The temperature on admission was 103.5°, and for the first four days ranged from 99° to 103°. From September 1st to the 9th it was normal—10 days. From the morning of September 10th to noon of the 13th there was a gradual rise to 104°. The fever persisted until the 25th. The spleen was readily palpable, and there were doubtful rose-spots on the skin of the abdomen. But for the relapse, we might have been in doubt as to the nature of the original attack, which (in the Hospital) consisted of four days of fever without rose-spots. An interesting point was the existence of a characteristic typhoid odor, which, with the history of three weeks' illness and the enlarged spleen (together with the absence of malarial parasites in the blood), seemed to settle the diagnosis.

Frank S., aged 24 (Hosp. No. 8254), admitted September 25th, 1893, on the 6th day of fever. The attack was severe, and he had 32 baths before the temperature fell below 102.5°. On October 9th and 10th the temperature touched normal, and from the 11th to the 14th there was apyrexia—4 days; then the fever recurred, and on the 15th reached 103.5°. The fever ran high, 104°–105°, and he had 41 baths in the relapse. The fever persisted for 16 days—became normal on the 30th. The spleen was palpable, and there were rose-spots.

Tertia W., aged 22 (?) (Hosp. No. 8488), admitted October 24th, 1893, on the seventh day of the fever. Primary attack severe; seventy-five baths; temperature range from 103°–105.5°. The temperature became normal on the 41st day—November 28th. Apyrexia from the 41st to the 64th day. The patient up and about. On December 20th a slight rise in temperature; on the 22nd and 23rd chills, with fever to 106°. Pyrexia, with enlarged spleen, rose-spots and severe constitutional symptoms from December 20th to January 28th. Apyrexia—complete—from December 29th to March 11th, inclusive—*42 days*. Pain in abdomen, fever, and a second relapse of fourteen days' duration, the temperature rising to 104°. There were no characteristic spots, but the tongue was furred and the general condition of the patient was that of typhoid fever. The patient left the Hospital on April 23rd, just six months after admission.

John S., aged 21 (Hosp. No. 10071), admitted June 9th, 1894. Duration of illness doubtful; he has been feeling badly for a month. The temperature range was from 103°–104°; the baths had a very marked influence, and each time reduced the temperature to normal or sub-normal. On the evening of the 15th, the 7th day after admission, the fever disappeared. There had been no diarrhœa; the tongue was furred, the spleen was readily palpable, but there were no rose-spots. There was a distinct diazo-reaction in the urine. For eleven days the temperature was normal. The spleen could still be felt. On the 24th he sat up in bed, and on the 26th he had meat. On the 27th and 28th the temperature rose to 102°. The tongue became coated, and the face was flushed. The diazo-reaction, which had disappeared from the urine, returned, and on the 29th he had three soft movements. On the 30th and July 1st the fever rose to 104.5°, and the baths were resumed. There were no rose-spots. On the 9th day of the relapse the temperature fell to normal, and the convalescence was uninterrupted.

Charles S., aged 18 (Hosp. No. 10517), admitted July 30th, 1894, on the 8th day of the fever. The temperature rose to 106°, and remained high for several days. From August 3rd to 6th he had involuntary movements of the bowels, with blood in moderate amounts. There was no diarrhœa. He improved rapidly, and on August 7th the evening temperature was normal. Then for six days the temperature was between 98° and 99°, on the 8th and 9th reaching on several occasions 100.5° and 101°. On the 10th, 11th, 12th and 13th there was practically no fever. In sixteen hours—from 4 a. m. to 8 p. m.—on the 14th the temperature rose from 98.2° to 105.6°—nearly eight degrees—without a chill. He had had egg that day, and his mother had given him a piece of banana. The fever persisted; the tongue became coated and dry, the spleen enlarged, but no rose-spots appeared. From August 15th to September 3rd the patient had irregular fever, after the first few days of a markedly remittent character; there were daily variations of from three to five degrees. The convalescence was protracted, and he did not leave the Hospital until September 27th.

Ella C., aged 11 (Hosp. No. 10658), admitted August 11th, 1894, on the 7th day of the fever. To August 24th she had thirty baths; the temperature range was 103°–104°. The spleen was enlarged; no spots. From the 24th to the 28th the temperature fell gradually. For six days there was no fever, except for a few hours on the morning of the 2nd, when the thermometer registered 101.5°. On the 4th, 5th and 6th the fever rose, and on the morning of the 7th reached 104.2°. The baths were resumed. On the 13th the temperature touched normal; then for a week there was an intermittent fever, with excursions from 97.5° and 98° to 100.5° and 101°. From September 23rd to October 3rd there was a daily slight fever to 100°. In the relapse the spleen became palpable, but no rose-spots were noted. The diazo-reaction was well marked in the relapse; it was not present in the original attack.

Maggie W., aged 19 (Hosp. No. 11070), admitted October 7th, 1894, after an illness of one week. The temperature was irregular, ranging for the first three days between 99.5° and 103°. Shortly after admission it rose to 104.5°. After the 10th it fell, and on the

12th touched normal. The spleen was not enlarged; there was no diarrhœa; the diazo-reaction was only found on one day; the spots were doubtful. From the 13th to November 1st—seventeen days—there was apyrexia, and the patient was up and about the ward, having gained in weight and was looking very well. At midnight, November 1st, the temperature rose to 100.5°, and by 8 p. m. on the 2nd was 103.5°. The fever kept between 102° and 103.5°, twice reaching 104°. On the 14th it fell to normal. There was no diarrhœa; the spleen was not enlarged; no spots were seen, and the diazo-reaction was not present. In spite of the absence of these, the character of the first attack, the complete apyrexia, the gradual onset of the fever, its persistence for fourteen days and the complete convalescence give a picture unlike anything but a relapse.

Eva M., aged 25 (Hosp. No. 10836), admitted September 10th, 1894. She was a Lithuanian, and could not be understood; but the persons who left her at the Hospital said that she had been ill in bed for two weeks. From the 10th to the 22nd there was fever only three or four times above the bathing point (102.5°). There was a faint diazo-reaction; doubtful spots were seen; the spleen was not palpable; there were no abdominal symptoms. The appearance was that of typhoid fever, and the tongue at first was coated and dry. There was dulness at the base of the left lung, with râles and blowing breathing; sputa negative. From the 22nd to the 29th there was no fever—seven days; then a rise gradually to 104° and a fever of nine days' duration. There were no spots; the spleen was not palpable; there was a faint diazo-reaction. Fever, increased heart's action and furred tongue were the only symptoms.

Charles W., aged 21 (Hosp. No. 11024), admitted October 2nd, 1894, about the end of the third week of fever. The temperature ranged between 103° and 104°; the drops after the baths were marked; the spleen was palpable, and on the 10th the temperature was normal. On the 11th, 12th and 13th the temperature was between 97° and 99°. On the 14th, 15th and 16th there was a gradual rise to 103°, and then for a week he had constantly temperature between 102.5° and 103.5°. The fever did not leave until the 30th. There were no fresh rose-spots; the spleen was palpable, and the tongue was coated.

John S., aged 20 (colored) (Hosp. No. 11102), admitted October 9th, 1894. He had been ill for four weeks, but he was so dull and stupid that it was difficult to get any accurate information. Until the morning of the 12th it was not thought that he had a specific fever, as the temperature did not rise above 99.5°. For the next week it ranged from 99° to 103°–104°. The tongue was furred; there was no diarrhœa, but a diazo-reaction was present. The spleen was not palpable. The fever fell slowly, and by the 31st the temperature was normal. For five days the morning and evening records were below 99°; then, on the evening of November 4th, the temperature began to rise, for a day or two not reaching beyond 102°, and on the 8th and 9th touching 103° and 104°. The tongue was furred, but the spleen was not palpable. On the 12th the temperature was normal; on the 13th and 14th there were slight rises, and subsequently the temperature remained normal.

This patient may have been admitted in an interval between two febrile periods. He looked as though he had had an illness, and the muscles were weak; but his tongue was quite clean, and there were no abdominal symptoms. Subsequently an interval of five days separated two periods of fever—one of nineteen, the other of seven days.

William H., aged 28 (Hosp. No. 11212), admitted October 23rd, on the 18th day of fever. The tongue was furred, the spleen was enlarged, but there were no spots and no diazo-reaction. The attack was mild, and by November 4th the temperature was normal. On the 5th it rose slightly, and then remained normal until the 13th—eight days. From mid-day on the 13th to the 24th there was fever of slight range, not rising above 102.5°. The tongue was furred, the spleen was enlarged, but there were no spots. There was no diazo-reaction, and the patient had no abdominal symptoms.

Albert G., aged 31 (Hosp. No. ——), admitted February 5th, 1895, about the 10th day of the fever. The attack was severe and typical; he had thirty-five baths, and by February 21st the temperature was normal. He sat up in bed on March 2nd; out of bed on the 4th. The temperature remained normal and sub-normal from February 21st to March 13th—twenty-one days. On March 13th, 14th and 15th the temperature rose a fraction of a degree each day, reaching 102.1° at 10 p. m. on the 15th. On the 16th and 17th it once or twice touched 102.5° and twice registered normal. On the evening of the 17th the temperature was 103.5°, and the fever persisted for just three weeks, rising to 103° and on several occasions to 104°. On the 21st day of the relapse the normal point was reached. The tongue was furred; there were no abdominal symptoms; the spleen, which was felt in the original attack, could not be palpated; there were a few suspicious spots. The convalescence was slow. On April 4th he complained of a general tenderness of the skin, which was moist.

The days of apyrexia were as follows:—9, 11, 10, 4, 23, 11, 4, 17, 7, 3, 5, 8, 21. One case had two well-marked relapses; 23 days' interval separated the original attack from the first relapse and 42 days the first and second relapses.

RELAPSE.—DOUBTFUL CASES.

Charles S., aged 25 (Hosp. No. 8930), admitted January 5th, 1894. For ten days the fever was very slight, and did not reach the bathing point. The spleen was palpable, and there were a few rose-spots. There was no diarrhœa. On the 15th, 16th, 17th and 18th the temperature touched normal and rose in the evening to 100° and once to 101°. Then, from the 19th to the 21st, there was a gradual ascent to 104°, and the patient became much worse. The diazo-reaction was not present until after the 19th. The spleen enlarged and there were successive crops of rose-spots. The temperature did not reach normal until February 5th.

In this case four days of normal morning temperature separated a very mild attack from one of considerable severity.

Henry L., aged 29 (Hosp. No. 9697), admitted April 18th, 1894. Fever moderate—103°–104°; only thirty baths. Fall gradual, and at 2 a. m. on May 7th the temperature was normal. Until 12 midnight it remained normal. On the evening of the 8th it was 101.5°, and on the 9th and 10th it rose gradually, touching once 104°. On the 11th, 12th and 13th there was a gradual fall, but it was not until the 19th that the morning and evening temperatures were normal; so that, after a period of complete apyrexia of thirty-six hours, there was a recurrence of the fever, five days about and above 102°, and then a gradual fall. The spleen was still enlarged; he complained of headache; there were no abdominal symptoms, and on the 16th, when the temperature was not above 100°, two doubtful spots were seen.

Emile G., aged 14 (Hosp. No. 10335), admitted July 9th, 1894. Severe attack; seventy-three baths to July 28th. Enlarged spleen; no definite spots; no diarrhœa. From July 28th to August 1st the temperature was between 100° and 101°, falling once below normal. From August 1st accession of fever—104°–104.5°—baths causing drops to 98° and 97°. High and persistent fever of nine days' duration; spleen enlarged; distinct rose-spots *for the first time.* From the 9th to 15th of August gradual fall of fever to normal, followed by uninterrupted convalescence.

Walter J., aged 26 (Hosp. No. 10426), admitted July 19th, 1894. The patient was a soldier, and had been in bed, in hospital at Fortress Monroe, for thirty-two days with headache, fever and weakness, but he had not had diarrhœa. When admitted his temperature was 99°, but in the evening it rose to nearly 103°. The edge of the spleen was palpable, but there were no spots. From the 19th to the 25th the fever only twice rose above 102°. On the 21st there were some suspicious rose-spots. From the 25th to August 11th the fever was higher, 103°–104°—and he had baths steadily. The spleen was enlarged, but there were no fresh rose-spots. The diazo-reaction, which was not present on admission, became well marked. On August 11th, 12th and part of the 13th the temperature was below 100° most of the time, and the tongue became clean and he felt better. From the 13th to 15th the fever again rose, and until August 2nd kept between 103° and 104°, requiring constant baths, of which he had to the latter date ninety-four. On August 17th typical rose-spots were seen, and they recurred. The tongue became furred, but the general condition kept good. The diazo-reaction was present, and the spleen remained large. From August 2nd to 12th the fever fell slowly to normal. From August 13th to October 3rd the temperature ranged from 99° to 100° and 101°, and twice rose for a few hours to between 103° and 104°, the last time on October 4th, the day on which he sat out of bed.

Counting the time in which the patient was in bed at Fortress Monroe, the fever lasted one hundred and ten days. It is very probable that on admission he was in an interval between two attacks, though we do not know that the fever had been down for any length of time. The three days from August 11th–13th separate clearly two febrile periods in the Hospital, and in the interval the tongue cleared and he looked much better. The spleen, however, did not reduce in size.

The case belongs to a group of great interest, in which two or three periods of high fever are separated by intervals of mild pyrexia of 99° to 100° and 101°.

Robert H., aged 20 (Hosp. No. 11963), admitted February 3rd, 1895, on the 14th day of his fever. The temperature range was high for a week—104°-105.5°. He had baths and then ice sponges. An acute pleurisy, with effusion, developed shortly after admission, but caused no symptoms and gradually disappeared. From February 3rd to March 11th there was continuous fever. Between the 10th and the 18th the fever fell gradually, and on the morning of the latter date fell below 99°. From the 18th to the morning of the 24th the temperature at some part of the day was below 99°, but rose to 100° or 100.5° in the afternoon. Then followed a period, from the 24th to March 11th, in which there was a mild fever—100° to 102°—only once reaching 102.5°. The spleen did not enlarge; there were no rose-spots, no diazo-reaction in the urine. He had a few sweats. There was no leucocytosis. The pleural effusion gradually disappeared. He had no diarrhœa. He had soreness of the legs, of a very indefinite character, and tenderness of the toes. Was it only a prolonged lysis or did the period from the 18th to the 24th, during which the temperature touched normal, separate the original attack from a relapse?

3.—POST-TYPHOID ELEVATIONS OF TEMPERATURE.

In eleven cases there were well-marked transient elevations of temperature during convalescence. Eighteen instances were given in the first Report.

Case XIX.—Augusta H., aged 42 (Med. No. 3168), admitted August 8th, 1893, in the beginning of the third week. The temperature became normal on the 27th, and remained so until September 7th. She had done very well. On the 6th she had her first meal of meat and potatoes. The tongue was not furred, and she had no abdominal tenderness. The fever rose to nearly 104°, and did not fall to normal until the morning of the 9th. During the 9th and 10th there were again slight elevations. The spleen became palpable, but there were no rose-spots. She convalesced slowly, and was afebrile from the 11th to the 27th. She sat up on the 17th, and on the 26th had solid food. The bowels had been a little relaxed. The temperature rose on the 27th, and on the three following days remained between 101° and 103°. There was slight abdominal pain, particularly on pressure, in the right iliac fossa. On October 1st, 2nd, 3rd and 4th there were slight oscillations of temperature. The spleen did not enlarge, and there were no rose-spots. The abdominal tenderness disappeared. The convalescence was very slow.

Case XX.—Emil E., aged 19 (Med. No. 3225), admitted at the end of the first week. On the 20th day—September 10th—the temperature was normal, and remained so until the 15th. He had been constipated. He had not had full diet, but had had milk toast on the 13th. On the 15th the temperature rose to 102°, and for five days ranged from 99° to 102.5°. The tongue was clean, the abdomen not tender; the spleen had not increased in size, and there were no spots. On the 21st and 22nd the temperature was normal, and he was given solid food on the morning of the 23rd. In the evening the temperature rose to 105° without a chill, and remained high all night in spite of two cold baths. By 6 p. m. on the 24th the fever had disappeared, and remained normal.

Case XXI.—John R., aged 45 (Med. No. 3484), admitted November 15th, 1893, in the 3rd week of his illness. The temperature for the first few days was not high, but he subsequently had thirty-eight baths, and on December 5th the fever had gone. He sat up on the 17th, and gained in weight rapidly. On January 1st, without a chill, the temperature rose to 104°. He had complained in the evening of pain in the side, but there was no fever. "This morning he complains of a catch on the right side when he takes a deep breath, and on auscultation there are a few fine crackles at the end of inspiration." The fever kept above 102° on the 1st and 2nd. On the morning of the 3rd it was normal, but rose to 103.6° in the evening. After the 4th he had no fever. The local signs at the right base did not extend, and he made a satisfactory recovery.

Case XXII.—Florence M., aged 22 (Med. No. 3406), admitted October 19th, 1893, on the 6th day of the fever. The attack was severe. The temperature fell below 100° on November 6th, and from the 9th to the 20th was normal. She had meat on the 18th. Between the 20th and 22nd the fever rose gradually to 104°, and remained above 101° until the 25th, becoming normal on the evening of the 28th. The abdomen was tender, and the bowels were a little loose. There were no fresh spots, and there was no increased enlargement of the spleen, and, without these, the fever alone, though of eight days' duration, seemed scarcely to justify the diagnosis of relapse. She developed delusions, and the case is referred to again.

Case XXIII.—George W., aged 22 (colored) (Hosp. No. 7910), admitted August 11th, 1893, in the third week of the fever. The temperature was high and continuous, and he had hæmoglobinuria. The temperature became normal on August 26th, and remained so until September 3rd. He had been given milk toast on the 31st, but had not been sitting up. From the 3rd until the 8th the temperature ranged from 101° to 103°. The tongue was furred, but there was no diarrhœa, and he did not complain of abdominal pain. The spleen was palpable, and had been so through the convalescence. He sat up on the 19th, and the recovery was uninterrupted.

Case XXIV.—Emma E., aged 16 (Hosp. No. 8264), admitted September 26th, 1893, with a mild attack of fever. During convalescence she had an attack of severe pain in the right leg, and the temperature for four days ranged from 100° to 102°. The fever was probably associated with the pain in the leg.

Case XXV.—Cecilia S., aged 24 (Hosp. No. 10803), admitted September 6th, 1894. Severe attack; prolonged fever. The temperature fell to normal on September 27th. On October 6th and 7th, after eight days of apyrexia, the temperature rose nearly to 102°, and for forty-eight hours did not fall to normal. The rise followed the eating of fruit, which had been given her by friends.

Case XXVI.—Charles R., aged 27 (Hosp. No. 10854), admitted September 11th, 1894. High fever; severe attack. The temperature fell to normal about October 10th, after having ranged for two weeks between 99.5° and 100.5°. He sat up in bed and ate meat on the 13th, and on the 18th sat up in a chair. He seemed to be doing very well in every way. On the afternoon of the 19th the temperature rose to 102.5°, and remained between 100° and 102° until early on the morning of the 22nd, and then for three days there were slight fluctuations between normal and 100°. The tongue was clean, the bowels regular, and nothing was found to account for the three days of fever.

Case XXVII.—Harvey S., aged 25 (Hosp. No. 10975), admitted September 26th, 1894, at the end of the first week of fever. For a week the temperature ranged high, once nearly to 106°, but there were no special features, and on October 5th, 6th, 7th and 8th the temperature touched normal each day. On the morning of the 8th the fever rose to 102.5°, and on the 9th to 104°. There were exactly forty-eight hours of fever, after which it disappeared completely.

The case is interesting since a period of four days in which the fever was not continuously normal was followed by what appeared to be a very characteristic post-typhoid recrudescence.

Case XXVIII.—Christopher T., aged 19 (Hosp. No. 11009), admitted October 1st, 1894, in the third week of the fever. The fever fell on the 10th, and he entered upon a satisfactory convalescence. On the 28th the fever rose, and on the 29th reached 103.5°. On the evening of the 30th it fell to normal. The rise was due to a follicular tonsillitis. Streptococci were obtained in pure culture.

Case XXIX.—Michael S., aged 22 (Hosp. No. 11392), admitted November 14th, 1894. The attack was severe, with high fever. The lysis was protracted for about fourteen days—from November 28th to December 11th; the temperature remained between 99° and 102°. On the mornings of the 11th and 12th it was normal. At 8 p. m. on the 12th the temperature was 100.5°. During the morning of the 13th it rose to 103°, and throughout the day kept high. On the 14th it remained about 101°, and fell to normal in the evening. It did not rise subsequently above the normal. There was nothing found to account for the elevation. It is interesting as separated by a very brief interval of apyrexia (scarcely, indeed, for an entire day) from a very prolonged lysis after a severe attack.

4.—TYPHOID FEVER AND MALARIA.

A careful examination is made of the blood in every patient with fever admitted to the wards, without which some of the cases of autumnal malarial fever could not be differentiated. A full analysis of our malaria cases for five years has been given by Drs. Thayer and

Hewetson in Fasciculi 1–5 of this volume of the *Reports*. Typhoid and malaria are the most common fevers of this vicinity and the patients come from the same localities. As mentioned in our first Report on typhoid fever, there was no case in which the two diseases were concurrent. Several cases were given in which typhoid fever followed a few weeks after an acute attack of malaria, in one case in a short enough time to make it probable that the infection with the former had occurred before the latter had disappeared.

In the following remarkable case severe typhoid fever followed a continuous malarial fever:—

Kate I., aged 31 (Hosp. No. 11331), admitted November 6th, 1894. The patient had been discharged from the Hospital October 7th, 1894. The history of her illness at that time is as follows:—

The patient was admitted September 28th, 1894, complaining of pains in the back and sides, and fever. She had malarial fever severely in February, 1894. She has as a rule been very healthy and strong.

Her present illness began on September 23rd with headache and fever, since when she has had a rigor every day, with fever and sweats. She has had nausea, but has only vomited three or four times. The attack came on suddenly when she was in good health, though she has had irregular dull pains about the limbs for some time. The examination of the blood in the dispensary was negative. Temperature on admission was nearly 104°.

She was a large framed, stout woman. Tongue was clean; there were no herpes; pulse soft, not dicrotic. There were no rose-spots; the spleen could not be felt. The temperature reached 105° at 6 p. m., fell throughout the morning, and was 100° at 8 a. m. At 7.30 p. m. the blood was again examined and was negative.

On the 29th there was a marked diazo-reaction in the urine, the only occasion on which it was present. The temperature rose at 2 p. m. to 104.6°. In the evening pigmented leucocytes and a hyaline malarial organism were found by Dr. Thayer.

On the 30th and October 1st the temperature ranged from 101° to 103°. She had no chills; the spleen was not enlarged, and she felt very comfortable.

We were still in doubt as to the nature of the attack, though in the morning examination of the blood on the 30th there was a well-marked intra-cellular amœboid hyaline body. On October 1st the temperature reached 103°.

On the 2nd there were perfectly characteristic hyaline malarial parasites seen, each containing small fine pigment. Quinine was administered on October 2nd. She felt very well; temperature gradually fell, became normal on the 4th, and on the 7th she felt well enough to leave the Hospital. On the 7th it was noted that the blood has been negative since the 2nd, and that no crescents had developed.

The organisms present were those associated with the irregular autumnal malarial fever.

On admission, November 6th, the temperature was 104°, and rose in the evening to 106°. She was a well nourished woman, a trifle pale; rational; pulse, 120; respirations, 30. There were well marked rose-spots on the abdomen, and the spleen was enlarged and palpable. The blood examination was negative. On the 6th, 7th and 8th the fever was high, rarely falling below 104°. From the history we were in doubt as to the nature of the disease, and baths were not begun until the 7th; they had very little influence. On the 9th she had grs. xv of Quinine, hypodermically. At 4.30 p. m. on the 7th, when the temperature was 105°, she had a chill, not severe, the only one during her stay in hospital. Until November 14th the fever kept continuously high, rarely going below 103°, even after the baths. She was drowsy, the tongue was furred, the rose-spots characteristic, and the spleen enlarged. The blood examination showed no changes. On the 12th and 13th she had slight diarrhœa. From the 14th the fever was less intense, and on the 19th, after the forty-sixth bath, it touched normal for the first time. On the 22d it rose again to 104°. From the 24th to the 27th the temperature was normal; at 8 a. m. on the morning of the 28th, the temperature was 99.4, and during the day rose to 103°. She then had a continuous fever for six days, the maximum temperature, 104.7°. She had no chills, no sweats. The general condition was good. The tongue was clean; the mind clear; there were no abdominal symptoms; the spleen could not be felt and there were no rose-spots. The diazo-reaction was not present. From December 4th to the 7th the temperature was normal; then, until the 27th, there were daily irregular elevations to 101°, 102°, and 103°, usually in the afternoon between 4 and 8 p. m.; the morning record being below 100°, and after the 20th below 99°. With this the general condition was excellent; her spirits were good; she craved food constantly; there were no features other than the fever. Most careful examinations were made of the blood but no organisms were found. After the 27th the temperature remained normal, and she was discharged well on January 12th.

5.—COMPLICATIONS AND SEQUELÆ.

Digestive System.

(*a*). Parotitis.

The only instance among the 160 cases is given fully at p. 345. It was really the development of this condition which suggested the diagnosis. The clinical diagnosis is as follows:—Illness of two weeks duration before admission; moderate fever; enlarged spleen; rigidity of muscles of neck and of right arm; mental dulness and delirium; cutaneous hyperæsthesia and increase of the reflexes; small amount of blood in the urine; no diazo-reaction; for three days before death normal temperature; parotitis.

In the six years.—Five cases occurred in the previous series of 229 cases, which with one in the present series, makes 1.54 per cent. in the 389 cases.

(*b*). Hæmorrhage from the Bowels.

In twelve cases hæmorrhage occurred. Three proved fatal, two of them from perforation.

In most of the cases, it will be noted, the bleeding was very slight, and in no case did the fatal result follow directly upon a profuse hæmorrhage.

In the previous series there were eight cases; so that in the 389 cases the percentage with hæmorrhage was 5.1.

Olaf J., aged 24 (Hosp. No. 7992). A severe case with protracted and high fever. He had been constipated. On the 15th day of the fever, at 1.45 a. m., on September 1st, the patient passed 250 cc. of pure blood, and in a short time after there was a second movement containing the same amount. He had no diarrhœa after it. There was no reduction in the temperature, and the general condition was not aggravated.

Alice C., aged 18 (Hosp. No. 7602), on the 16th day of an attack of moderate severity, after the 32nd bath, passed a stool containing clots, not very abundant and not large. She had not had diarrhœa.

Charles H., aged 31 (Hosp. No. 7955), on the 23d day of a severe attack, after the eighty-second bath, passed a stool in which were about ℥ iv of clotted blood. The bowels had been a little loose. The hæmorrhage did not recur.

George S., aged 34 (Hosp. No. 8287), on the 17th day of a very severe attack, had a soft movement containing clots of blood. He had had diarrhœa and much abdominal distension. He had a very prolonged attack with relapse, but there was no further hæmorrhage.

Florence M., aged 22 (Hosp. No. 8448), had on the 13th day a small hæmorrhage, which was found in the draw-sheet. She had had no diarrhœa, but the abdomen had been distended. As the next stool contained no blood, the baths were resumed after a single sponging.

John W., aged 24 (Hosp. No. 9566), admitted April 3rd, on the 8th day of illness. On April 12th he had a soft stool, intimately mixed with blood, with one or two small clots. Shortly after he passed a second stool containing still more blood. The fever did not drop after either stool. He had been having one or two soft movements each day. He was ordered lead and opium pills. No further bleeding occurred. The baths had already been omitted on account of the intense bronchitis.

Charles S., aged 18 (Hosp. No. 10517). The case is given fully among the relapses. The attack began severely; temperature rose to 106°. There was no diarrhœa, and the abdomen was not tense. At 3.30 a. m. on August 2nd he passed an involuntary stool containing blood, with very little fæcal matter. On August 3rd he passed another stool containing small clots and dark reddish-brown material. On August 4th he had another small hæmorrhage. The hæmorrhages occurred without diarrhœa and had no injurious influence. After August 4th the temperature fell, and he improved rapidly.

Homer H., aged 29 (Hosp. No. 11074), admitted October 8th, 1894, on the 10th day of the fever. The temperature ranged between 103° and 104°. There was a copious rose rash. On the 11th and 12th the temperature had been below the bathing point. On admission he had slight diarrhœa; then, on the 11th and 12th, one stool each day. At 4 a. m. on the 13th he had a stool consisting of almost pure blood. There was no pain; the temperature only fell one degree. On the 18th the temperature fell to normal, and he made a rapid recovery.

Joseph M., aged 20 (Hosp. No. 11235), admitted October 25th, 1894, on the 6th day of the fever. The onset was with severe vomiting and diarrhœa. The temperature ranged during the first week between 104° and 105°; often the maximum number of baths had to be given in the twenty-four hours. The spleen was large and the rose-spots were abundant. At 11 p. m. on the 29th, after the eighteenth bath, the patient had a hæmorrhage, passing about half a pint of bright blood, not clotted, and mixed but slightly with fæces. It did not affect the temperature in the slightest, which remained between 103° and 104.2° until 8 a. m. At 7.30 a. m. he had another slight bleeding. The abdomen was not distended, and the general condition was good, though the tongue was brown and fissured. On the 30th, the stool passed at 7 p. m. contained about 150 cc. of dark, tarry blood. The stool at 3 p. m. on the 31st contained dark fæcal matter, but no blood. By November 6th the temperature touched normal, and he made an uninterrupted recovery.

(c). PERFORATION.

In the previous series there were eight deaths from perforation; in this series five, a percentage of 3.1.

For the six years.—389 cases, with thirteen deaths from perforation, 3.3 per cent. The records are given at p. 473 in the study of the fatal cases.

Probable perforation, recovery.—Occasionally the symptoms suggest perforation of the bowel, and for a time the patient is desperately ill; but gradually the serious features disappear, and we are in doubt as to the underlying condition.

H. A. H., aged 23 (Hosp. No. 10449), admitted July 22d, 1894, about the end of the first week of fever. The temperature ranged from 102.5° to 104.5°; the spleen was palpable, the rose-spots were distinctive and the general condition very good. There was no diarrhœa, and the abdomen was not distended. At 8 p. m., August 2d, the temperature was 103°, and he had a bath; and for the following forty-eight hours he was distinctly better. At 7 p. m. on the 3d he complained of a sudden pain in the right side, at the lower ribs. The abdomen was held tense, and there was tenderness on pressure in the right hypochondriac and lumbar regions. During the night the patient complained but little of pain, after a hypodermic injection of morphia, but the pulse became very weak and rapid, and the expression of the face was noted by the nurse to have changed, and he seemed dazed.

On the morning of the 5th, Dr. Thayer made the following note: "Patient is lying on his back with the eyes sunken and rolled upwards; the face is pinched and drawn, and the expression very suggestive of peritonitis. The hands are cold and the fingers blue. The abdomen, which was previously relaxed and sunken, is now distended, and the muscles are tense and contracted. The liver flatness is obtained upon the 6th and 7th ribs. The note is the same over the entire abdomen on direct percussion, and on auscultatory percussion the 'tap' is everywhere conveyed directly to the ear. The pulse is 128 and small. The second sound at the base of the heart is reduplicated."

The temperature was 104° at 10 a. m., and through the day did not rise above 102°. There was no diarrhœa. He had profuse sweats. On the 6th the fever was higher, 103°–105°, and the pain was still severe. At 6 a. m. he had a large soft yellow stool. He was given strychnia hypodermically, and spirits of turpentine by mouth. The facial expression was better, and the pulse stronger. On August 7th the fever was lower and the abdominal pain and distension much less. The perspiration was profuse.

August 8th. He had a comfortable night and was in all respects better. The temperature did not rise above 102° and the abdominal pain had disappeared. On the 9th the serious symptoms had had all disappeared, and he made an uninterrupted recovery.

Ambrose B., aged 31 (Hosp. No. 11310), admitted November 4th, at the end of the 2nd week of an attack of fever. The temperature was high, 104°–104.5°; the rose-spots were present and the spleen was palpable. He had diarrhœa on admission; but from the 10th to the 18th there were only one or two movements daily. On the 14th he began to complain of pain in the abdomen, but nothing could be made out beyond slight soreness on pressure. On the 15th there was considerable distension, the soreness was more marked, and the right leg was drawn up. In the evening the temperature rose to 105.5°, and the pulse to 126. He had vomiting through the night, and in the morning (16th) looked badly. The abdomen was distended, extremely sensitive and tense, particularly in the right iliac fossa; so that palpation was very difficult. The liver dulness was not obliterated in the nipple line. There were only three movements in the 24 hours. The patient was extremely nervous, quite rational, and the pulse though rapid was of fair volume. He was ordered turpentine enemata. The vomiting had ceased. For the next three days the abdominal distension continued, he had occasional vomiting, but the pulse did not rise above 120 nor the temperature above 104°. On the 18th he had five stools, and on the 19th six, all fluid, yellow in color, and in one, on the 18th, there was about a drachm of bright blood. The tongue was furred, but not dry. The great distension and soreness prevented any satisfactory examination of the abdomen. There was no increased micturition; the right leg was now not so painful, and could be extended. From the 20th, there was decided improvement. The fever lessened, the diarrhœa checked, and the abdominal pain and distension were relieved. The chief enlargement of the abdomen had been above the navel, and on the 22nd coils, in peristalsis, were seen in this part. Palpation could now be made more readily and the chief region of soreness was in the right iliac fossa. The temperature fell gradually and after a protracted convalescence the patient was discharged January 5th.

The intense abdominal pain, the distension, the vomiting, and the rapid pulse suggested perforation. The general condition, however, the facial expression (which was never Hippocratic), the extremely nervous state of the patient, the absence of a progressive character in the symptoms, made us doubt the existence of a general peritonitis. The tenderness in the right iliac fossa, the flexion of the right leg and the persistent soreness in this region after the symptoms had subsided, make it possible that there had been perforation of the appendix.

Vascular System.

PHLEBITIS.

Thomas T., aged 36 (Hosp. No. 8667), on the 35th day of a very severe attack, while the temperature was still ranging as high as 103.5°, began to complain of pain in the left groin. The note on December 22nd reads as follows:—"There is tenderness in the left groin, and slight superficial redness. It does not appear to be a glandular enlargement, but there is a fulness in Scarpa's space. The vein is not to be felt. There is œdema and pitting on the left tibia. He cannot flex the left thigh upon the abdomen." Subsequently, a cord developed along the inner aspect of the thigh in the position of the long saphenous vein. On the 24th the superficial redness in Scarpa's space persisted; but the œdema of the leg had disappeared. He had no further trouble from it. This patient had chills at intervals from the 3rd to the 8th weeks. He had none in the 5th week when the symptoms of thrombosis were present.

John E., aged 26 (Hosp. No. 8509), towards the end of a relapse, in the sixth week, had swelling and tenderness in the left groin and an induration just below the saphenous opening. Scarpa's space looked fuller on the left side, but there was no swelling of the leg. Movement of the leg caused pain. A thrombus developed in the long saphenous vein, but did not extend to the femoral. He had a slow, tedious convalescence. There was no aggravation of the fever while the leg was painful.

Theodore B., aged 24 (Hosp. No. 10298), admitted July 5th, 1894, at the end of the second week of fever. From the 12th to the 15th the temperature ranged between 99° and 100°. On the evening of the 15th it rose to 104°. On the 16th he began to complain of pain in the inner part of the left thigh. There was no redness, no swelling, but a well-marked cord could be felt in the course of the internal saphenous vein. On the 16th and 17th the temperature kept up. From the 18th to 22nd it was almost normal. On the morning of the 22nd he had a chill, and on the 26th the temperature rose again to 104°. There was no sign of redness in the course of the saphenous vein, the thrombus in which could be well felt. The general condition was excellent, and he made a good recovery.

H. A. H., aged 23 (Hosp. No. 10449), admitted July 22nd, 1894, at the end of the first week of fever. On August 14th, when the fever was below 102° and he was improving in every way after a severe attack, he had a sudden pain in the left leg. On the 15th the thigh and leg were swollen and tender, and the calf was very hard. The internal saphenous vein could be felt in its entire length. There was no increase in the fever, which remained between 101° and 102°. On the 16th the leg was less swollen, but there was still tenderness along the inner aspect of the thigh. Within a few days this had disappeared, and he recovered completely.

Respiratory System.

PLEURISY.

Onset of Typhoid Fever with Acute Pleurisy—so-called Pleuro-typhoid.

Pleurisy is not a frequent complication of typhoid. There were only two cases in the previous series. In 53 autopsies at the Montreal General Hospital, acute pleurisy was present twice, and empyema once. The complication is usually late, but the first case here given illustrates the form of typhoid fever which sets in with an acute pleurisy,—the pleuro-typhoid of the French.

Julia H., aged 19, admitted to Ward G of the Johns Hopkins Hospital, September 21st, 1893, complaining of a severe pain in the left side. Her family history is good. As a child she had many ailments,—measles, typhoid fever (?), small-pox and pneumonia. Since puberty she has been very well, with the exception of an attack of ague.

Present illness. For nearly a month she has not been feeling very well, and she has had weakness and sometimes nausea. Nine days ago she had a shaking chill, which lasted about ten minutes, and was followed by fever and sweating. Next day she felt well enough to be up and about, but she had nausea and headache. Since that time she has had a slight cough. Yesterday morning she had a very severe pain in the left side (made much worse by taking a deep breath), and fever and cough, for which symptoms she sought relief.

On admission the temperature was 101°; the pulse, 112°; respirations, 32. The blood examination was negative; leucocytes, 1500 per c. m.

Present condition. The patient is a healthy looking, well nourished girl. At the time of the examination she was sweating, and cried out a good deal with pain on being moved. The temperature on the morning of the 22d rose to 104°; the tongue was coated and red at the edges. The thorax was well-shaped; the expansion very much more on the right than on the left side. On drawing a deep breath she complained of great pain in the left axillary region. Percussion was clear in front on the right side; on the left side there was modified resonance at the fourth rib; below the fifth rib, and extending into the axilla, flatness. Behind, there was flatness from about the angle of the scapula. The breath sounds in the infra-scapular region were somewhat distant, not tubular; no râles. In the lower axilla, as she drew a deep breath, there was a loud friction murmur. At the base behind, tactile fremitus was diminished. Only a small amount of gelatinous sputum was obtained; no tubercle bacilli; there were a few encapsulated micrococci. The abdomen was smooth, not distended; spleen not enlarged. Patient was ordered warm applications to the chest and a Dover-powder at night.

On the 23rd and 24th the temperature ranged between 102° and 103.5°; respirations from 35 to 42, and the movements caused great pain as she drew a deep breath or coughed. There was very little expectoration and it was not blood-stained.

25th. The patient looked very ill—more so, indeed, than is usual in a case of ordinary pleurisy, but there was no evidence of any additional trouble, and every day rose-spots were looked for carefully and the expectoration was examined. The range of temperature was higher and the prostration rather more severe than are common in simple acute pleurisy.

On the 26th the temperature ranged from 103° to 104.5°, and at this morning's visit there were seen for the first time some distinct rose-spots. The area of splenic dulness appeared to be somewhat increased downwards; the edge could not be felt on account of the soreness on pressure at the costal margin. She was ordered baths to-day at 70° F. The condition in the left pleura remains unchanged. The friction rub is still loud in the lower axilla and there is a good deal of pain. For the next week the patient had the well-marked features of severe typhoid fever; the temperature range was between 104° and 105°, and the baths had very little influence, rarely reducing the temperature more than one or two degrees. She retained consciousness, but the pulse was rapid, constantly above 120 and often very feeble. The spleen was easily palpable on the 30th. On October 5th, after having had 56 baths, she seemed to be so feeble and reacted so badly that it was thought advisable to stop them, and on the 6th and 7th she was sponged. The temperature remained between 103° and 104°, and on the 7th began to fall, and for the first time since her admission reached 101°, and on the 8th 100.5°. From this time on the fever fell rapidly, and on the 13th was normal and remained so. The condition of the left pleura gradually improved.

On October 5th the breathing was noted as still distant, and the friction sound was well heard in the axilla.

On the 6th it was noted that the resonance was still defective below the angle of the scapula. Fremitus, however, was more distinct, and in the axilla the friction sound was not nearly so loud. The cough was not so troublesome.

On the 13th it was noted that the dulness at the left base had almost disappeared; the friction sound persisted. After this she made a very satisfactory recovery; had no trouble during convalescence and gained between November 2nd, and November 18th, when she went out, nearly nineteen pounds in weight. The friction persisted until the first of November, when the condition at the left base was practically normal. In addition to the whiskey, which she required freely, she was given while the pulse was very rapid and feeble strychnia in doses of a thirty-second of a grain.

It is interesting to note in this case that in spite of the frequent bathing—56 baths between 10 a. m. on the 26th of September, and 12 noon on the 5th of October, just ten days, an average of five a day—the pleurisy progressively improved and the cough was not aggravated. The condition when we stopped the baths was very critical; thus on the 3rd it was noted after one of the baths that the pulse was 160, respirations 48. The tongue was tremulous and dry; but she took the food and stimulants, and with the sole exception of great tenderness of the toes in consequence of the baths she made an uninterrupted recovery.

Acute Pleurisy at Onset.

Jacob G., aged 35 (Hosp. No. 10139), admitted June 16th. A well-marked friction rub was present in the left axilla. He has had no particular pain in the chest. There is a diffuse bronchitis. He had a mild attack; the pleurisy disappeared in a few days.

Acute Pleurisy with Effusion in the Third Week.—No Symptoms.

Robert H., aged 20 (Hosp. No. 11963), admitted February 3rd, 1895, on the 14th day of the fever. The attack had begun with a chill and nausea, but he had neither cough nor pain in the side. On February 5th a friction rub was noted in the right lower axillary region. He had no pain, no cough. In a few days there were well-marked signs of effusion. On the 12th the line of dulness behind had reached the angle of the scapula; an exploratory puncture brought away a clear, brownish fluid, which was sterile. He had profuse sweating. For the first week the fever was high—103°-105°. The effusion cleared gradually, and by the time he left the Hospital—March 31st—the resonance was only a little defective. There were no symptoms pointing to the pleurisy.

INTENSE BRONCHITIS.

In *Case XXVI* of the fatal cases the bronchitis was so intense and the cyanosis became so extreme that bleeding was employed.

Renal.

URINE.

In *Volume IV*, a very thorough consideration of this secretion in typhoid fever was given by Dr. Hewetson. The examinations are made daily in the severe and at short intervals in the mild cases. An interesting study of Pyuria and its associated micro-organisms, by Dr. Blumer, will be found in another part of this fasciculus.

Albumin was present in 139 cases. In only five of these was it abundant; in a majority there was only a distinct trace with the usual tests, such as is almost invariable in the fevers.

Tube Casts were present in 61 cases, usually only a few and sometimes found only after the use of the centrifuge.

There were no cases of serious nephritis in the series, such as were present in the first.

Diazo-reaction.—This was present in 118 cases—about 74 per cent. Its importance, &c., are fully considered by Dr. Hewetson in Vol. IV.

HÆMOGLOBINURIA.

George W., aged 22 (Hosp. No. 7910), admitted August 11th, 1893, complaining of diarrhœa and fever. He had been ill for nearly three weeks with headache, diarrhœa, fever, and a 'weakness' in the belly. He had no hæmorrhages, and no bleeding from the nose. The temperature on the evening of admission rose to 104°. The pulse was dicrotic 108. The color was good, and his general condition satisfactory. The urine first passed was coffee-colored, sp. gr. 1022, and contained albumin and many granular tube casts. The edge of the spleen was palpable. The abdomen was a little distended, but not tender. The fever for the first ten days ranged from 101° to 105°. On the 12th and 13th he had seven baths, but they were omitted (on account of the condition of the urine) from the 13th to the 17th.

The amount of urine ranged from 800 to 1200 cc. It was reddish brown in color, specific gravity about 1020, and contained much granular débris and many tube casts, but no red blood corpuscles. The urine gave all the usual reactions for blood-coloring matter, but in the numerous examinations made between the 11th and the 17th, no red-blood corpuscles were seen. By the 20th, the urine had cleared, and was yellow brown in color, no longer turbid, and contained only a trace of albumin, but no blood and no tube casts. On the 22nd the color was normal, and there was only a faint trace of albumin. The baths were resumed at noon of the 17th, and he took twenty-six before the temperature fell below 102.5°. He convalesced rapidly, with the exception of a recrudesence of five days duration. The blood examination, made repeatedly during the first few days, showed no malarial organisms. On September 9th the urine still presented a trace of albumin but there were no tube casts.

Cutaneous System.

(*a*). HERPES LABIALIS.

Theresa H., aged 24 (Hosp. No. 8594), had, on the 25th day of her illness, a well-marked crop of herpes on the lips.

Henry L., aged 29 (Hosp. No. 9697), had on May the 5th, as the fever was declining, an herpectic eruption on the upper lip.

(*b*). GENERAL ERYTHEMA.

Heinrich W., aged 12 (Hosp. No. 8369), before taking baths had a diffuse erythema on chest and abdomen, which persisted for two days.

Charles S., aged 18 (Hosp. No. 10517), had, on admission, a general erythematous blush upon the trunk; no rose spots.

(*c*). BOILS.

During the 4th year, throughout the autumn of 1892, there were many examples of boils during convalescence. At one time there were seven or eight cases in Ward F.

During the 5th year there were very few cases. One patient, Evans (Hosp. No. 8029), with a very mild attack, had, late in convalescence, a large boil in each axilla.

Chas. B., aged 17 (Hosp. No. 10563). The attack was severe, with high fever and delirium; twenty-six baths. Crops of boils began to appear before the fever had fallen; there were many small ones on back. Later, a large boil developed on outer aspect of right thigh; cultures showed a pure growth of staphylococcus aureus.

(*d*). URTICARIA.

Theodore B. (Hosp. No. 10298), during convalescence had an extensive outbreak of urticaria on both forearms, unassociated with any error in diet.

(*e*). POST-TYPHOID ABSCESS.

William P., aged 22 (Hosp. No. 8145), admitted September 11th, 1893, on the 8th day of the fever. The temperature ranged from 102° to 104°, and fell to normal on the 25th. On the 25th an abscess was opened between the buttocks and a considerable amount of pus escaped. Cover slips showed a coccus as the predominating organism, but in culture both the colon bacillus and the staphylococcus albus were isolated.

Olaf J., aged 24 (Hosp. No. 7992), admitted on the 4th day of the fever. The attack was very severe, and the baths had very little influence on the fever. On the 15th day he had a slight hæmorrhage from the bowels. The temperature became normal on the 30th day. In the sixth week a large abscess developed on the left side of the sacrum, which was opened and packed with iodoform gauze. The temperature did not rise during the formation of the abscess. Cover slips from the pus showed only a coccus; in culture the staphylococcus albus and s. aureus, and also the streptococcus pyogenes, were separated.

Heinrich W., aged 12 (Hosp. No. 8369), admitted October 9th, 1893, on the 7th day of the fever. The temperature did not fall to normal until the 37th day. On November 1st a small area of redness and swelling was noticed in the right iliac region, just at the site of a well-marked rose-spot; by the 3rd it had pointed and there was fluctuation. A small abscess was opened on November 8th. Cultures showed a pure growth of the staphylococcus aureus.

Gaulius F., aged 21 (Hosp. No. 9321), admitted March 2nd, 1894, on the 4th (?) day of the fever. The temperature became normal on the 22nd day. The note on March 13th reads as follows: "For several days the toes in the right foot have been painful, and on the dorsum there is a well-marked blush, and it is tender and hot to the touch." On the 14th the blush persisted, and the plantar surfaces of the toes were very tender. There was some puffiness on the dorsum. The left foot was not affected. We thought at first that the condition was the usual 'tender toes' which so often follow the baths. On the 16th the swelling had extended, and the redness and œdema reached almost to the ankle joint, but they did not extend over the entire width of the dorsum. The toes are very sensitive. By the 19th the swelling was greater and fluctuation was evident. The temperature reached normal on this day. The abscess was opened and about ℥ ii of pus removed. The cultures showed a pure growth of the staphylococcus aureus. About the 13th the patient had also pain in the right ear and tenderness over the mastoid process. On the 17th there was a watery discharge from the ear, and he had no further trouble. The fever did not rise again after the 19th.

Thomas T., aged 36 (Hosp. No. 8667), whose case is fully given in the article on *Chills in Typhoid Fever*, p. 452, during convalescence, on the 75th day, more than two weeks after the fever had subsided, had redness and swelling over the inner malleolus of the right leg.

For a day or two it looked as though it was an acute periostitis, going on to suppuration; but it subsided under the use of cold applications, and he had no further trouble.

Nervous System.

(*a*). THROMBOSIS OF LEFT MIDDLE CEREBRAL ARTERIES.

See *Case XXXIII* of the series of fatal cases.

(*b*). INSANITY.

Florence M., aged 22 (Hosp. No. 3406), admitted October 19th, 1893; she had no initial delirium. The attack was severe, and the baths did not influence the fever very much. There was a good deal of abdominal distension. The fever disappeared about the 26th day. November 14th.—"Three days ago the patient began to have various delusions; as that she had had money left her; that she had had visitors; and that another patient wished to cut her throat. She sings and talks to herself when left alone." November 20th.—"She is not in the least melancholic, but is always in a most cheerful mood. She thinks now that she is to be operated upon. Subsequently she became somewhat melancholic. She developed a very tender back, which seemed to improve her mental condition. She gradually got better and left the Hospital well, January 7th, 1894.

(*c*). CATELEPSY.

Betty G., aged 27 (Hosp. No. 8616), admitted on the 21st day of the illness. The fever for a week ranged from 103° to 105°. She was tremulous, noisy, and was with difficulty kept in bed. The day after her admission, she would not answer questions, but lay with the eyes shut, the eyelids quivering, and the arms and legs remained in any position in which they were placed. The next day she seemed clearer in her mind, and the cateleptic features were not again seen.

(*d*). EPILEPSY.

Annie M., aged 15 (Hosp. No. 9611), had had for seven years epileptic fits, recurring every few weeks. She was admitted on the 8th day (April 7th), and had a tolerably severe attack, the fever falling about the 20th day. From the onset of the disease to April

30th, she had no fit. On this day, after the temperature had been normal for ten days, she had a severe convulsion.

(*e*). HYSTERIA.

Alice C., aged 18 (Hosp. No. 7602), during convalescence from a severe attack, had on July 12th an hysterical outbreak, with much crying. She had been very well with the exception of the tender toes which had troubled her very much.

(*f*). THE PAINFUL BACK OF TYPHOID FEVER (TYPHOID SPINE).

In the first Report I gave a short account of the condition to which Dr. Gibney gave the name 'Typhoid Spine' and reported several characteristic cases.

The following additional cases are of interest, particularly the second and the third in which the symptoms were milder and less enduring.

M. S., aged about 35, admitted February 19th, 1895. He had been in Ward F. from November 14th to December 15th, with typhoid fever, a very typical attack. He was, however, very restless and nervous, and became so obstreperous in the baths that after the third day cold spongings had to be substituted. Before the patient was discharged, he complained of soreness in the back when stooping and in walking, and for this the Paquelin cautery was applied. He says that this has been persistent, and has become much worse in the past six weeks, so that he has been quite incapacitated. On admission, he looked pretty well, but had a worried expression. There was no fever. He walked very stiffly, the body a little inclined forward, and he hesitated with each step. He was quite unable to stoop; and any jar caused pain. On attempting to straighten the back there was pain of a dull aching character. The examination showed a perfectly straight spinal column, and the spines of the vertebræ were not tender on the firmest pressure. Lateral and dorsal flexion could be made, but ventral flexion could not be made without pain, and the act of twisting was difficult. There was slight soreness in the sacral region, particularly over the sacro-iliac synchondroses. There was no disturbance of sensation; he flushed easily, was very nervous, perspired readily, and the hands and feet were usually cold and moist. He was given the tincture of nux vomica in large doses, and the Paquelin was applied lightly on the lower dorsal region on several occasions with much benefit. He improved very slowly, and left the Hospital nearly well.

The following cases are of interest as illustrating milder forms of this trouble, and in one the pain began and was for some time localized in the neck.

Florence M. (Hosp. No. 8448), whose case is given under the sections of insanity and post-typhoid elevations, on December 16th, after she had been sitting up for nearly a week, began to complain of severe pain in the back, which was much increased by any sudden jar or after walking about. The examination was negative, and there was no pain on pressure. On the 17th and 18th the pain was too severe to allow her to sit up. It continued to trouble her for more than a week. There was no disturbance of sensation or of motion in the legs. On the 27th she sat up, and after this she improved rapidly; and when she went out—January 7th—the tenderness in the back had almost disappeared.

Christopher T., aged 32 (Med. No. 3228), had sat up on October 4th, when convalescent from a relapse. On October 6th he began to complain of pain in the back of the neck, particularly in the upper part. There was no swelling. The soreness persisted and was very troublesome; the patient could not turn his head from side to side. The Paquelin cautery gave him much relief. Nothing could be felt on examining the cervical vertebræ from the pharynx. Subsequently the soreness extended to the back and down the hips. He held himself very erect and walked stiffly. He said that he was more comfortable while up and moving about. There were no tender points, and the movements of twisting and bending were not painful. The free application of the Paquelin gave great relief, and at the date of his discharge—October 21st—he was very much better.

(*g*). PAINFUL LEGS.

During convalescence patients are often very weak and 'groggy' in the legs, and it may take months before they feel well and strong in walking. In protracted cases, when the patient first sits up and begins to go about, there may be in addition œdema of the feet and legs. Thus, Thomas T. (whose case is given fully in the article on chills, p. 452), during the prolonged convalescence, after he got up and moved about, had œdema of the feet and legs and much stiffness in walking.

There is a condition of 'painful leg' after typhoid fever in which there is much soreness in one or both calves, without redness, without evidence of neuritis, and without signs of thrombosis in the veins. Of the six cases here given, the soreness in all developed after the fever had disappeared. In five of the cases the condition was unilateral. In *Case VI* both calves were very tender. The most suggestive feature is the marked soreness of the muscles on pressure and on movement, resembling very much that which is so pronounced in neuritis, and which was present in several of the cases reported in the special article on the subject in this fasciculus. It did not seem to me that the features were sufficiently pronounced to place these cases in that section, the symptoms indeed point rather to a *myositis*, but until we have further knowledge it is best to speak of the condition under the caption above given.

Case I.—Sophie S., aged 24 (Hosp. No. 8090), during convalescence from a mild attack, complained greatly of pain in the left popliteal space, and of stiffness in the leg. There seemed to be a little fulness in the space, but it was not tender on pressure. There was no clot to be felt in either the saphenous or femoral vein, and there was no swelling of the ankle. The soreness and stiffness persisted for ten days or two weeks, but no local features developed to account for it.

Case II.—Emma E., aged 16 (Hosp. No. 8264), in the second week of convalescence from a mild attack, complained a great deal of pain in the calf of the right leg which seemed a little swollen, particularly between the heads of the gastrocnemius muscle, and was very sensitive on pressure. No thrombus could be felt. The ankle was not swollen. With this there was a slight rise in temperature for four days. The leg was wrapped in cotton wool. The extreme sensitiveness persisted for five or six days, and subsided without giving any indication of the nature of the trouble.

Case III.—Annie M., aged 15 (Hosp. No. 9611), admitted April 7th, 1894, at the end of the first week of fever. She had had from the outset much pain in the left leg, particularly in front, and on motion. It was also tender on pressure, but there was no swelling or redness. The baths were not begun until the 9th. She had much pain in the leg, none in the popliteal space, but entirely in front, and on the 9th she complained of soreness over the dorsum of the foot. There was no tenderness of the toes and no shooting pains or numbness. She had the tubs regularly, and by the 12th the pains had disappeared.

Case IV.—George T., aged 29 (Hosp. No. 8104), admitted on the fifteenth day of a severe attack. He had sixty-one baths. During the first week of convalescence he had much soreness in the calf of the left leg. There was neither redness nor swelling, and the tenderness was in the *muscle*, not in the skin. The knee jerks were slightly increased. The condition persisted for a week or ten days, and at the time of his discharge—a month after its onset—he still felt soreness in the muscles of the left calf.

Case V.—John W., aged 26 (Hosp. No. 9566), sat up May 1st, 1894, on the 35th day of a very severe attack. On May 9th the calf of the right leg was found to be swollen and tender, chiefly in the muscles. He had been complaining for a few days of soreness in the legs. He had also slight tenderness on pressure in the left calf. He kept about, and gradually the swelling and pain disappeared. There was no evidence of thrombosis in the veins.

Case VI.—Thomas A., aged 42 (Hosp. No. ——), admitted April 2nd, 1895. The fever was moderately high, and he had forty-eight baths. On April 15th, before the temperature was normal, he began to complain of tenderness of the toes, chiefly in the plantar surfaces, but slightly also on the dorsum and on the under surface of the heels. After he had been up for ten days he began to complain of great soreness in the legs. There was no œdema, nor any redness or swelling; on standing and when moving the muscles felt sore. To the touch the skin was not sensitive, but on pressure upon the calf muscles he winced at once. On May 16th, on attempting to stand, he almost fell; any effort to stand caused severe pain in the calves. There were marked fibrillary tremors in the muscles of the calf of the right leg. He was ordered to bed and to have cold applications. For ten days, without any loss in muscular power, this painful condition persisted. There was no tenderness of the nerves.

TENDER TOES.*

During the 5th year there were only four cases with great tenderness of the toes,—all had had baths, one case twenty-five, two over fifty, and one sixty-two. In one case the tenderness was more diffuse than usual, and extended to the soles of the feet. In three cases it developed before the temperature had reached normal. During the 6th year there were only three or four cases, all presenting the usual characters.

Special Senses.

OTITIS.

Harris G., aged 24 (Hosp. No. 8600), admitted November 10th, 1893. The temperature was high—105.5°—and the general symptoms were severe. On November 14th there was a profuse discharge from left ear; the mastoid process was not tender. The submaxillary gland on this side was a little enlarged. The cover-slips from the discharge showed only a lance-shaped diplococcus, occurring in pairs or chains. Cultures in agar showed only one organism which corresponded in all particulars to the micrococcus lanceolatus. The discharge subsided, and gave no further trouble.

Theresa H., aged 24 (Hosp. No. 8594), admitted November 9th, 1893. On November 14th, about the end of the third week, there was a discharge from the left ear. There was slight tenderness. There was not much pain; the discharge continued for more than a week. The note as to cultures was mislaid and not added.

Gaulius F.—Given under post-typhoid abscess.

Charles B., aged 17 (Hosp. No. 10563), admitted August 6th, 1894. Severe attack; high fever, delirium, etc. On the 8th it was noticed that the patient had an offensive discharge from both ears. This he had had from infancy, but it became much aggravated during the early days of his fever.

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*See Vol. IV, p. 69, of the *Reports.*

Ambrose B., aged 31 (Hosp. No. 11310), admitted November 5th, 1894. Severe otitis media, with purulent discharge during the height of the fever. Dr. Blumer isolated the bacillus pyocyaneus and two other undetermined organisms.

Locomotor System.

ARTHRITIS.

Frank H., aged 16 (Hosp. No. 11108), admitted October 10th, about the end of the first week. He had in all twenty baths, and by October 24th the temperature was normal. It was a very typical case of moderate severity. On the 26th the note reads as follows: "The temperature was normal on the 24th. Yesterday and to-day there has been a slight rise—this a. m. to 102.5°. The left shoulder is swollen, red and painful, particularly at the very top of the joint. The swelling is general." In the evening the temperature was 104.4°. On the 27th the swelling and redness persisted, and the boy could not use the arm at all. Hot formentations had been applied, which gave a good deal of relief. On the 28th the condition was unchanged, but the temperature had fallen to normal. On the 29th a striking change had taken place, altogether within the twenty-four hours; the swelling had lessened, the pain was better, but there was still redness. The swelling subsequently localized just at the top of the acromion, but it gradually subsided, and after persisting for about ten days, disappeared completely.

III.—FIVE YEARS' EXPERIENCE WITH THE COLD-BATH TREATMENT OF TYPHOID FEVER.

BY WILLIAM OSLER, M. D.

During the first year of the Hospital service, typhoid fever was treated symptomatically. The number of severe cases admitted was unusually large, and there were eight deaths among thirty-three patients—a percentage of 24.2. For the past five years, ending May 15th, 1895, systematic hydrotherapy has been used—the method of Brand, with certain minor modifications. In the first *Report* (Vol. IV) the plan was given; but I may repeat here that each patient receives a tub-bath of twenty minutes at 70° every third hour, when the rectal temperature is at or above 102.5°. Frictions are applied in the bath, and a warm drink or a stimulant is given afterwards. In a large proportion of the cases no other treatment is employed. If the pulse is feeble whiskey is given, and strychnia. The diet is either wholly milk or in part broths, and egg albumen. It may be noted that all the cases come under my immediate care or, in my absence, that of Dr. Thayer, the Associate in Medicine.

In estimating the value of any plan of treatment, it is important that all circumstances should be taken into account. In the previous report I dealt with the statistics as so many patients admitted, of whom so many died; and this, I think, should be done in all Institutions—give the total number of cases of each disease treated to a conclusion, and the number of deaths, irrespective altogether of the length of stay in the hospital, or the condition on admission. General hospitals are everywhere liable to be repositories of the more severe or troublesome cases, and in typhoid fever more particularly of protracted cases, in which serious symptoms have developed late in the disease. A high rate of mortality in any given acute disease may be an indication of a special usefulness of the institution. As already given, the general statistics of the Hospital in typhoid fever are:—

Cases admitted during the six years ending May 15th, 1895,	389
Number of deaths,	34
Percentage of mortality,	8.7
Cases admitted before the introduction of hydrotherapy,	33
Number of deaths,	8
Percentage of mortality,	24.2
Cases admitted since the introduction of hydrotherapy,	356
Number of deaths,	26
Percentage of mortality,	7.3
Number of cases bathed,	299
Number of deaths in the bathed cases,	20
Percentage of mortality in the bathed cases,	6.6

The percentage 7.3 represents the total mortality during the past five years; but as it does not represent the mortality of the cases treated by hydrotherapy, the figures must undergo a further analysis. Many circumstances interfere with the systematic carrying out of the plan, among which the following are the most important.

In the first place, a number of cases are admitted in the second week, and even in the third week, with a falling thermometer, and the fever constantly below 102.5°. Cases, too, are admitted early, which have low temperatures and mild symptoms throughout. Brand and others urge that these should also be bathed; but in a large proportion of all such cases, this appears superfluous. There are exceptions, however,—cases in which the fever is low on admission, and even remains low for a week or ten days, to be followed by active and threatening symptoms. Nos. *XXII* and *XXIX* of the fatal cases were of this kind, and in both one could not but regret that the baths had not been used from the outset. In the very mild cases, seen more frequently in private than in hospital practice, the baths are unnecessary. Last year we admitted an unusually large number of such mild cases.

In the second place patients are admitted late in the disease, and are too ill to bathe. A patient brought in at the end of the third week, with high fever, rapid, feeble pulse, meteorism, and diarrhœa, stands, I believe, a much better chance, with careful sponging, to reduce the fever, than he does with tubbing every fourth or fifth hour and the disturbance unavoidable in the lifting out of bed. There were five patients admitted in too feeble a condition to bathe, not one of whom died.

Thirdly, there is a group of cases which on admission present serious complications—hæmorrhage, signs of perforation, very intense bronchitis, pneumonia, pleurisy or intense meteorism with severe diarrhœa. On account of hæmorrhage the baths were postponed on several occasions. There was no instance in which on admission the pulmonary symptoms seemed to contraindicate the treatment.

Fourthly, there are cases which were not bathed at first because the diagnosis seemed doubtful. Two of the fatal cases, to which reference will be made shortly, were not recognized clinically as typhoid fever. Each autumn we have a certain number of cases of malaria which present features closely resembling typhoid fever—so much so that baths have been given. These are instances of the so-called æstivo-autumnal fever, in which the organisms may at first be difficult to find. In other instances with a strong suspicion of malaria for a day or two, the symptoms of typhoid fever have developed subsequently, but the temperature meanwhile has fallen below the bathing point. In several cases the condition at first resembled tuberculosis.

And lastly, the baths have been frequently changed to cold sponges, on account of hæmorrhage, profound weakness, tenderness and swelling of abdomen, signs of perforation, and in a few cases because of the active protestation of the patient. The sponging, when thoroughly done, is almost as formidable a procedure as the cold bath; indeed, we have had patients ask to have the baths resumed.

The following are among the most important reasons which caused transient suspension of the method: Hæmorrhage, 13 cases; perforation, in which condition even the sponging is rarely allowable, but in which the extremities may be bathed without disturbing the patient; on account of great weakness and prostration, 11 cases; on account of active mental symptoms, for one day in one case, for two days in another; for extreme tenderness of the abdomen, for one day, one case; for severe bronchitis, for intense laryngitis, after operation on abscess of parotid, for severe phlebitis, for pleurisy, each one case.

In many of the fatal cases the baths were suspended for twenty-four, sometimes forty-eight hours before death.

There were several instances in which the symptoms of relapse were so slight that the treatment was not rigidly enforced.

Of the 356 cases treated during the five years, 299 were bathed, of these 20 died, a mortality of 6.6 per cent.

Of the 57 cases which were not bathed for various reasons, usually because of the mildness of the disease, six died, a percentage of 10.3. This high ratio of mortality in the unbathed cases is, of course, due entirely to the circumstance that conditions, mentioned below, interfered with the use of the baths in a group of cases of unusual severity. In the six fatal cases, the histories of which are given in full in another place, in two, *Cases XI* and *XVIII*, the diagnosis was wrong; in the one an old man of 70, with consolidation of the lower lobe, the disease was thought to be lobar pneumonia; and in the other, the patient had been in hospital the year before with entero-colitis, and on re-admission with severe diarrhœa, typhoid fever was not suspected.

In *Case XXVII* the disease was at first thought to be tuberculous cerebro-spinal meningitis—the temperature was low, the nervous symptoms marked, and it was not until parotitis developed that our suspicions were aroused about typhoid fever.

In *Case XXVIII*, after twelve days of moderate fever, severe symptoms developed, with tympany and abdominal tenderness and diarrhœa. It was thought best to use the cold sponges; death was probably due to perforation.

In *Case XXXII* the patient was admitted, bleeding profusely from the bowels, and

In *Case XXXIII* the fever was low, only touching 104° at entrance, and subsequently not rising to bathing point. Death occurred from thrombosis of the middle cerebral arteries.

Two advantages are claimed for hydrotherapy in typhoid fever—a mitigation of the general symptoms of the disease, and a reduction in the mortality. Our experience during the past five years bears out these claims.

In general hospitals, to which cases rarely are admitted before the end of the first week, the full benefits of the cold bath, as described by Brand, cannot be expected; nevertheless, in any large series, the severer manifestations appear to be less common. As has been urged so often and so ably by many writers, the beneficial action is not so much special and antipyretic as general, tonic, and roborant. The typhoid picture is not so frequently seen, and we may have twenty or more cases under treatment without an instance of dry tongue or of delirium among them. It is a mistake to claim, as do the too ardent advocates of the plan, that severe nervous symptoms are never seen. I have taken the pains to go over carefully our records on this point. There were in the first three years thirteen cases, in the past two years nine cases with delirium. Most of these were protracted cases which had from 75 to 120 baths.

A far more important claim is that the use of the cold bath reduces the mortality from the disease. The comparison of death rates as a measure of the efficacy of any plans of treatment is notoriously uncertain unless *all* the circumstances are taken into account. In our own figures for the past five years, for example, illustrate this—6.2 per cent. in the bathed cases, 10 in the unbathed cases—as the latter group is made up entirely of cases too mild to bathe and six patients in whom either the disease was not recognized or who were too ill on admission to treat.

Statistics have a value in this connection only when the figures on which they are based are numerous enough to neutralize in some measure their notorious mobility. Small groups of cases are useless; 24 per cent. of mortality in our first year in thirty-three cases, and a series of nearly fifty bathed cases without a death, illustrate the liability to error in discussing a few cases. Unfortunately, typhoid fever is a disease in which the cases may be reckoned by hundreds and thousands, and the average mortality in general and special hospitals throughout Europe and America is easily gathered. The rate may be placed between 15 and 20 in each hundred cases. In the Metropolitan Fever Hospitals, London, the death rate, as given in the Report for 1893, was 17 per cent.

The cold-bath treatment, rigidly enforced, appears to save from six to eight in each century of typhoid patients admitted to the care of the Hospital physician.

While I enforce the method for its results, I am not enamoured of the practice. I have been criticized rather sharply for saying harsh words about the Brand system. To-day, when I hear a young girl say that she enjoys the baths, I accept the criticism and feel it just; but to-morrow, when I hear a poor fellow (who has been dumped, like Falstaff, 'hissing hot' into a cold tub), chattering out malediction upon nurses and doctors, I am inclined to resent it, and to pray for a method which may be, while equally life-saving, to put it mildly, less disagreeable.

IV.—PYURIA IN TYPHOID FEVER.

BY GEORGE BLUMER, M. D.,
Assistant in the Medical Clinic.

The cases here reported have been under observation between September 1st and December 31st, 1894, and are those cases of typhoid fever which presented pyuria as a complication at one time or other in the course of the disease.

The cases number ten out of a total of sixty cases admitted between the dates mentioned, or very nearly 17 per cent. The histories of the individual cases will be found at the end of the report; that which follows is a general review of the results of their analysis:

The Appearance of the Pus.—The pus was sometimes present on admission, so that the day when it appeared could not be determined; in both of the cases in which this occurred the admission was before the twelfth day of the disease. Of the remaining eight cases the pus appeared in four between the 10th and 15th day; in three between the 22nd and 28th day, and in one on the 42nd day. It would seem then that whilst pus may appear at any period of the disease, it occurs most commonly either at the end of the second or in the fourth week.

With regard to the duration of time during which the pus was present, this varied largely; in one case it was only found for seven days; in two others it was still present on the patient's discharge, forty, and ninety days respectively having elapsed from the time of its appearance; in six cases it lasted from twenty to fifty-five days, and in the one fatal case it was only found on the day of death. The question of the duration of the pus is important from a prophylactic point of view, for, as we shall see later, the pus was always accompanied by, and presumably caused by, bacteria, the bacterium found being in some cases the typhoid bacillus; and when we consider the large number of bacilli excreted daily in such a case, we can realize the danger of infection from this source. The quantity of pus in the urine varied both in different cases, and in the same case at different times; as a rule there was a large quantity present in every case at one time or another. In only one case was the quantity noted as moderate when at its height, and in one other as small all through its course. The manner in which the pus appeared in the urine was not always the same; in some cases a few pus cells would be noted at first, and there would be a gradual increase to the maximum amount; in others a moderate amount of pus would appear suddenly, and in still others a very large amount would appear suddenly. By suddenly we mean within twenty-four hours, and this comparatively abrupt appearance is not very hard to explain in these cases. The amount of urine being as a rule diminished, the patient requires to urinate much less frequently than normally, and if bacilli are once introduced into the bladder, they have under these conditions an excellent chance to multiply. The conditions which govern the persistence of bacteria in the bladder are mechanical ones, and we know from experimental evidence that, though bacteria can readily develop in the normal bladder, they are washed away by the act of urination so frequently that they soon disappear; in fever, however, the urine is passed much less frequently than is normal, and is often only imperfectly discharged from the bladder, leaving a residue swarming with bacteria to contaminate the next urine discharged from the ureters.

In most of the cases under consideration the mode of onset was gradual, though in two of them a moderate amount of pus appeared suddenly in the urine, and in two a large amount.

The elements commonly associated with the pus in these cases were casts, epithelial cells and bacteria.

In three out of the ten cases casts were never noted in the urine, and in four others, though noted, they were only temporarily present, and were not associated with the pus, the latter appearing from four to twenty days after the disappearance of the casts.

In the three cases in which casts were associated with pus, one was a fatal case of the renal type in which the pus only appeared on the day of death; in the other two cases the casts were only noticed when a small amount of pus was present, and were absent when the amount of pus was at its height.

Epithelial cells were associated with the pus in 50 per cent. of the cases, but their presence was inconstant, and they were only noted when the amount of pus was small.

Bacteria were noted in the clinical examinations in three cases, in all of which they were present in very large quantities.

Mucus, blood and amorphous phosphates or urates were very occasionally found with the pus, and always when the quantity was small.

There appeared to be no relation between the appearance of pus, and the appearance of the rose-spots, as a rule, though in the one non-fatal case in which the typhoid bacillus was isolated the pus appeared about eight days after the last rose-spots were noted. This fact is mentioned because of Konjajeff's theory that the typhoid bacilli in urine are signs that lymphomata are present in the kidneys, these lymphomata appearing, according to this author, about the same time that the rose-spots appear on the skin.

There appeared to be no relation between the temperature, and the amount, or appearance of the pyuria; in two cases the pus was present from the beginning and persisted throughout the disease; in four it appeared when the fever was at its height, and in the remaining four either after it had disappeared or just as it was disappearing.

Albumin was present in the urine in all the cases, but never in more than traces, except in the fatal case; at times it was entirely absent in filtered urine, whilst the pus was present, and it usually disappeared coincident with the disappearance of the pus, though in two or three cases the albumin persisted a day or two after the pus had disappeared.

Sugar was never present in any case, nor was bile, except in the one fatal case.

The amount of urine was decreased, as is usual in typhoid, but there was no suppression of urine, except in the fatal case, and no definite relation between the amount of urine and the amount of pus.

The Bacteriology.—It is necessary to state, in regard to the technique, that none of the patients had been catheterized previously, so that cystitis from this source could be excluded.

The urine in each case was drawn per catheter with proper precautions, and plate cultures were made. The latest methods of differentiating typhoid from colon were used.

Bacteria were present in the urine in varying numbers: in some cases 1 cc. of urine would give only 10–30 colonies in a plate; in other cases one drop of the urine had to be diluted to obtain the colonies at a sufficient distance from one another for working purposes.

The following bacteria were isolated from the 10 cases, usually in pure culture:—

1. *The colon bacillus.*
2. *The typhoid bacillus.*
3. *The staphylococcus albus.*
4. *An unidentified coccus.*

The colon bacillus was present in seven cases—once in association with the typhoid, and six times in pure culture.

The typhoid bacillus was found twice—once with colon, and once alone.

The staphylococcus albus was found once in pure culture.

In one case an organism was found which was not identified. It was a medium-sized coccus, but did not give the reactions of the pus cocci. The organisms were small and oval, occurred in groups and stained well; they grew readily on the ordinary media, except potato, where an invisible growth occurred; did not liquefy gelatin, did not coagulate milk, produced acid, but no indol. The organism was non-motile.

The form of organism present in the urine did not, as a rule, influence the date of appearance, the amount or the duration of the pus.

It is noticeable, however, that the three cases in which bacteria were present in such large numbers as to be observed in a microscopical examination were all colon bacillus cases. In the case in which the unknown coccus was found pus was only present in the urine for seven days, all of the other cases running over twenty days.

Regarding the cases in which the typhoid bacillus was present in the urine, one was a fatal case of the renal type, the other an ordinary uncomplicated case, and it is interesting to note that in this case the pus did not appear in the urine until the 42nd day of the disease.

In looking over the literature of typhoid fever, we have been unable to find any work bearing directly on the subject of pyuria as a complication, though it is barely recognized as such in some of the larger text-books.

A review of the work which has been done on bacteruria in typhoid and on the urinary complications is desirable that we may, if possible, gain some idea of the origin and significance of the pyuria.

Wissicowich is the first one accredited with finding the typhoid bacillus in the urine in typhoid, and since his contribution Neumann and Konjajeff have done the most important work.

The frequency with which the bacilli were found in unselected cases varied considerably with various authors—Karlinski of Krakow claiming to have found it in 50 per cent. of the cases examined, whilst Hueppe only found it once in sixteen cases. Between these two sets of observations come other authors with percentages varying from 15 to 28. In the majority of these cases the typhoid bacillus was in pure culture.

Unfortunately all of these observations were made before the more exact methods of differentiating the typhoid from the colon bacilli were in vogue, and are therefore open to doubt. Judging from the results of the bacteriological examination of the ten cases just reported, it would seem probable that a large number of the bacilli designated as typhoid in these papers were really colon.

Besides these reports on the typhoid bacilli in urine we find other reports on the nephritic form of typhoid in which bacilluria was present; in these cases the typhoid bacillus is not always present, and when present is quite commonly associated with the pus organisms.

For the origin of the bacilli which cause the pyuria we must look to the pathological changes which have been found in the urinary organs.

The presence of the typhoid bacillus in the kidney is of common occurrence, either in connection with the so-called lymphomata, with distinct nephritis, abscess formation, or with no appreciable lesion other than the usual parenchymatous changes found in prolonged fevers.

Konjajeff, who has made a special study of the bacteriology of the typhoid lymphomata, always isolated the typhoid bacillus in pure culture from them.

Bouchard, in nine autopsies on patients who died with bacteruria during typhoid, demonstrated bacteria in the kidney substance in all cases and also lesions of the cells, such as are found with transient nephritides. His work, however, must not be regarded as conclusive, as he made no bacteriological study either of the urine or the kidneys, and the bacteria in both might just as well have been the colon as the typhoid bacillus.

Besides the typhoid bacillus other bacilli have been noted in the urine in typhoid fever, and in the kidneys after death.

Neumann isolated the streptococcus in two of his cases of bacteruria, and in the nephritic form of typhoid the pus organisms have been frequently obtained.

In typhoid nephritis and in abscess of the kidney following typhoid the colon bacillus and the pus cocci have both been found at times. We have been unable to find any case in which the colon bacillus was present in typhoid lymphomata, and in all the post-mortems here in which the lymphomata have been specially examined, the typhoid bacillus alone has been found. No cases of pure pyelitis, due to the typhoid bacillus, are reported.

The bladder has been found to show pathological changes in a fair number of cases, though in most of these the changes consist of submucous ecchymoses, which could be accounted for without assuming a bacterial origin, and which could hardly produce a pyuria.

In a few cases graver vesical alterations have been found, as patches of gangrene in the mucous membrane, or even gangrene of the entire mucosa, the most extensive observations on this subject having been made in 1843 by Cossy, a pupil of Louis.

Guinon has reported one case of cystitis following typhoid in which, in addition to pus, a pure culture of the colon bacillus was found in the urine; this case is, however, hardly comparable to ours as the cystitis followed directly on catheterization.

It would seem then from post-mortem evidence that the sources of the bacilli in the urine could be either the kidney or the bladder, and presumably the pus is from the same source as the bacteria.

This latter fact is, however, not by any means proven, as unfortunately the most of the articles on typhoid bacteruria fail to mention the state of the urine, other than that it contained albumin; only an occasional reference to a microscopical examination being found.

In the kidney the two sources of the bacteria are the lymphomata on the one hand and a definite nephritis on the other.

According to Konjajeff typhoid bacilli in the urine are definite proof of the presence of lymphomata, though the occurrence of lymphomata does not necessarily lead to bacilluria.

In the case of a nephritis Bouchard seems to think that the bacilli gain entrance to the urine by direct trauma of the kidney cells.

Whilst we have no direct evidence to prove that the pyuria in typhoid is ever due to bladder implication, we must admit that the cases of actual gangrene of the vesical mucous membrane were in all probability of bacterial origin, but further observation is necessary on this point. One other origin of the pyuria should be considered, and that is the intestinal origin.

It has been shown by experimentation, that by irritating the rectal wall in animals, and then introducing cultures of certain bacteria into the rectum, a cystitis is almost invariably set up, the organism having passed through the tissue between the rectum and bladder.

Whilst we do not ordinarily have implication of the intestinal tract as low down as the rectum in typhoid, yet a certain number of such cases do occur.

In one of our cases, in which the rectum was extensively involved in the pathological process, and in which, during life, both the colon and typhoid bacilli were isolated from the urine, only the typhoid bacillus was obtained from the kidneys at the post-mortem cultures; it is presumable, therefore, that the colon bacillus had some other place of origin than the kidneys in this case.

We must not forget, also, that cases of what were formerly believed to be post-mortem migrations of the colon bacillus into the organs are now pretty definitely proved to be ante-mortem, and occur often with the very slightest lesions of the intestinal wall.

It is easy to understand, then, how in a disease with as extensive intestinal lesions as typhoid fever the colon bacillus could pursue a similar course and thus gain entrance to the urine.

In the cases reported it would seem impossible to definitely state the origin of the pus and bacteria in the urine. The clinical picture was that of an ordinary typhoid fever, the pyuria giving rise to no special symptoms.

Nor does the state of the urine aid us: casts were often absent, and when present were not usually in intimate association with the pus; epithelial cells were present in some instances, but most authorities are agreed that the origin of epithelial cells in the urine cannot be definitely made out. The reaction of the urine will not help us, as we can have an acid urine in a cystitis as well as in a pyelitis or nephritis.

It would seem, then, that pyuria, whilst present fairly frequently in typhoid fever, is a complication of no gravity, and is only important from its association at times with the typhoid bacillus, prophylaxis demanding that in these cases the patient should be retained in the Hospital till the pus has disappeared.

The following is a resumé of the cases in which the pyuria occurred:

Case I.—L. H. J., aged 13, colored, school-boy, admitted to the Hospital complaining of cough and headache.

The family history is negative; the past history is negative.

The present illness began three weeks ago with weakness, not much headache, loss of appetite. The bowels were regular; no pain in the chest or abdomen. He has had cough, with white, frothy expectoration. The nose bled three or four days ago several times; no chills. The blood was negative for malarial organisms.

The patient was well formed, well nourished; the tongue was slightly coated. The lungs were negative, except for numerous coarse, moist and sibilant râles. The heart was negative; spleen was not palpable on admission.

The temperature, which was 103° on admission, ranged between this point and 104.6° for the first week, except when influenced by baths. It dropped slowly during the second and third weeks, and at the beginning of the fourth week had reached normal. It then, however, went up again, patient having a relapse, which lasted about three weeks.

The urine showed pus from the third day after admission. The pus decreased in amount as the fever went down, but never disappeared, the cells appearing again in great numbers when the relapse came on. At the time of discharge—forty days after the termination of the relapse—the urine had not contained any pus for a week.

Cultures in this case showed the bacillus coli communis only.

Case II.—G. E., aged 10, colored, school-girl, admitted to the Hospital complaining of headache.

The family history is negative.

She gives a history of having had, soon after birth, a purulent discharge from both eyes, and later a general eruption. The past history is otherwise negative.

The present illness began five days ago. The onset was gradual, with headache, listlessness and loss of appetite. On the second day of the disease the patient had a shaking chill, followed by fever and profuse sweating. She has had no chills since, but has constant headache and feels tired and sleepy. She has no cough; the appetite is gone; the bowels are constipated. She has had no nose bleed. The blood was negative for malarial organisms.

On admission the note states that she is a sparely nourished child; tongue thickly coated; pulse regular, good volume. The lungs are perfectly clear. The heart is apparently not enlarged, and the sounds are clear, except at the base, where a soft systolic murmur is heard; also present in both subclavians.

The abdomen was rather full, nowhere tender; splenic flatness extended from the eighth rib nearly to the costal margin, but the border was not palpable. The spleen was never palpable through the entire course of the disease.

The case was complicated about the middle of the third week by a double parotitis.

For the first eight days after admission the temperature ranged between 101° and 103.8°, except when influenced by baths. After this it fell steadily but slowly, and on the twenty-third day had reached 99.5°. It, however, rose again, patient having a relapse, which lasted about three weeks. The temperature never fell to normal, but remained between 99° and 100° for eight days following the first relapse, when a second relapse of lesser severity, and lasting nine days, occurred. The temperature then fell, and remained normal until discharge—two months after admission.

The urine contained a few pus cells from the beginning. They were, however, very scanty at first. They were most numerous during the height of the first relapse, and were still present in small numbers when the patient was discharged.

Cultures in this case showed the bacillus coli communis only.

Case III.—H. T., aged 31, male, native of Germany, baker, admitted to the Hospital complaining of having caught cold.

The family history was negative. Personal history was negative.

The present illness began about twelve days before admission with deafness. He had some abdominal pain, but none anywhere else, constant headache, and nose-bleed three or four times in the week before admission. The appetite has been poor; bowels have been a little loose. He gave up work about a week after the onset of the disease; has been in bed since. No cough. The history is unsatisfactory, as the patient is extremely deaf.

Note on admission says: Patient is a man of large frame, well nourished; tongue slightly coated; pulse full, soft, regular, dicrotic; lungs clear throughout. The heart is negative, except for a slightly accentuated second aortic. Splenic border palpable about 3 cm. below the costal margin. A number of suggestive spots on lower thorax and abdomen; one or two on the back. The next day the patient developed an extensive rose-rash.

The temperature ranged between 103° and 104° for the first five days, excepting when influenced by baths. After this it fell gradually with occasional slight rises, and reached normal thirty days after admission.

The urine contained pus from the seventh day after admission; at first in small quantities, but about the end of the third week enormous numbers of pus cells were present in the urine. The pus continued, but gradually decreased from about the fortieth day, and on discharge there was none present.

Cultures in this case showed the bacillus coli communis only.

Case IV.—E. E., aged 21, male, native of the United States, laborer, admitted to the Hospital complaining of abdominal pain.

Family history negative.

Past history.—Had malaria of the tertian type two years ago. Denies venereal history.

The present illness has lasted for about ten days, but he has been able to work up to within six days ago. The illness began with headache, pain across the back, and general aching. He has had no chills, no nose-bleed, no cough. Appetite very poor; bowels loose, two to four movements daily; no blood in the passages; pain in the abdomen, not very severe. Blood examination negative for malarial organisms.

The note on admission stated.—Patient is a man of small frame, sparely nourished; tongue is coated; pulse full, regular, dicrotic; lungs clear throughout; heart negative, except for an accentuation of the second aortic; border of spleen just palpable. There are several suggestive spots on the lower thorax.

Temperature for first twelve days ranged very irregularly between 97° and 103°, being very markedly influenced by baths. After this it fell gradually and reached normal twenty-three days after admission.

The urine contained pus from the twenty-third day after admission. It continued up to within eight days of discharge, at which time the microscopical examination of the urine was negative.

Cultures in this case showed the bacillus coli communis only.

Case V.—S. O., male, aged 20, native of the United States, farmer, admitted complaining of a heavy feeling in the chest.

Family history.—Comes from a house in which eight of the thirteen inmates have either had or are now suffering with typhoid fever. One sister and one brother have lately died from the disease.

Past history.—He has had the usual diseases of childhood; denies venereal disease.

The present illness began about five days ago; onset gradual; felt tired and giddy; no chill; slight headache and nose bleed. Appetite absent; bowels loose—two or three movements in the twenty-four hours; no blood in the stools; no cough. Examination of the blood for malarial organisms negative.

On admission the note is: Patient well developed, well nourished; tongue slightly coated; lungs clear throughout; heart not enlarged; at the apex a harsh systolic murmur, transmitted to the axilla, and heard also over the body of the heart. The second aortic sound is accentuated. Spleen is just palpable; no rose-spots.

Patient had a slight attack of hæmorrhage from the bowels; the disease otherwise ran its usual course.

Temperature ranged between 101° and 104°, except when influenced by baths, for the first week, after which it gradually dropped, and reached normal by the eleventh day after admission. It remained at normal, with the exception of a sudden rise, lasting over a part of the twenty-four hours, on the twenty-second day.

Pus was observed in the urine in slight amount on the seventh day after admission, it remained only for a few days and then disappeared. On discharge microscopical examination of the urine was negative.

Cultures in this case showed an unidentified coccus, more fully described in another portion of the article.

Case VI.—C. W., male, aged 47, Irish, laborer, admitted to the Hospital complaining of headache and pains in the legs.

The family history was negative.

Past history.—Has used alcohol and tobacco excessively; denies venereal disease.

The present illness began about five days ago with tired feeling and a severe headache, which have continued ever since; no nose-bleed; no chill; pain in the epigastrium, dull and constant; no cough; has general pains. Appetite is absent; bowels constipated. Examination of the blood on admission for malarial organisms was negative.

Note on admission states.—Patient was a small framed, fairly nourished man; tongue slightly coated; pulse small, low tension, regular, not dicrotic. Percussion over the lungs is clear. On auscultation the expiration was prolonged, and everywhere accompanied by occasional wheezing or piping râles. Heart negative. The spleen was just palpable. There were one or two suspicious spots on the abdomen and lower thorax. The disease ran its usual course.

The temperature for the first sixteen days ranged between the normal and 104°, except when influenced by baths. After this it gradually dropped and reached normal by the eighteenth day, but rose again the same day, reaching 102.6° four days later; then falling again and reaching normal seven days from the beginning of the second rise.

The urine showed a few pus cells from the fifth day after admission. These gradually became more numerous until the thirty-fifth day after admission, when they began to decrease, and at the time of discharge, on the 29th day of January, 140 days after admission, pus had been absent for nearly sixty days.

Cultures in this case showed the colon bacillus only.

Case VII.—C. R., male, aged 33, Pole, laborer in Iron foundery, admitted to the Hospital complaining of fever.

Family and personal history both negative.

Patient has been ill four weeks, with headache and fever; has not been able to work for three weeks; no chills; no nose-bleed;

some cough, but no expectoration. Appetite good; state of bowels not ascertained. Patient does not speak good English. Blood on examination was negative for malarial organisms.

Note on admission states.—Patient looks ill; expression is dull and heavy; moderately well-nourished; tongue is moist, slightly furred; pulse is regular, not dicrotic. Heart and lungs are both negative. The spleen is not palpable. There are several rose-spots present on the abdomen.

The temperature, which reached 103° shortly after admission, fell gradually and had reached normal by the end of the fifth day.

The urine began to show small amounts of pus on the tenth day after admission. The amount gradually increased, but never became very great. Pus was still present at the time of discharge, three weeks after admission.

Cultures in this case showed the typhoid bacillus in pure culture.

Case VIII.—J. S., male, aged 24, Hungarian, laborer, admitted to Hospital complaining of fever.

The history was very difficult to obtain, as the patient spoke neither English nor German. He has been ill about two weeks with headache; no nose bleed; no chills; slight cough, but no expectoration; has loss of appetite and pain in the abdomen; bowels are loose.

On admission the blood was negative for malarial organisms.

Note on admission states: Patient is a healthy-looking, well-built, muscular man; tongue has a white fur. Pulse is quiet, not dicrotic; lungs clear, except for a few bronchial râles at the bases. The heart sounds are clear. There is a very extensive rose rash over the lateral region of the chest and abdomen; also a few on the arms. The spleen is readily palpable.

The temperature for the first seven days ranged between 100.5° and 104°, except when influenced by baths. After this it fell gradually, and reached normal about fourteen days after admission.

The urine contained a few pus cells on the ninth day after admission. On the eleventh day more pus cells were noted, and it was also observed that the urine was swarming with bacteria. The pus continued until within four days of discharge, but on the day before patient was discharged microscopical examination of the urine was negative.

Cultures from this case showed the colon bacillus only.

Case IX.—J. R. A., male, aged 20, German, sailor, admitted to the Hospital complaining of pain in the abdomen.

Family history is negative.

Past history.—Has had malaria two years ago; no details; had urethritis a year ago.

Present illness began about a week ago, with gradual onset; no chill. There was diarrhœa, six or eight stools in twenty-four hours, loose, watery, never bloody, which ceased after four or five days; no nose-bleed; cough for a week with moderate white, frothy expectoration; headache at times. Appetite poor; feels weak at times. Blood on admission was negative for malarial organisms.

Note on admission.—Patient looks dull and apathetic; tongue dry, coated; sordes on the lips; pulse slow and regular, quite dicrotic. Lungs clear, except for a few moist râles at the bases.

Heart.—Point of maximum impulse apparently in fifth space about in the mammillary line, relative dulness at the third rib, does not pass the left sternal margin. At the apex the first sound is soft, much prolonged, almost like a murmur. As one passes upwards a well marked systolic murmur is heard, more marked over the pulmonic area. This is a little rough and probably organic. The spleen is readily palpable. There is very profuse rose-eruption on the trunk, arms and thighs. Temperature for first three days after admission ranged between F. 99° and F. 103°, except when influenced by baths, it then gradually fell, ranging between F. 99° and F. 101°, until the seventh day after admission, when it reached normal.

The urine showed a large amount of pus four days after admission, and on the fifth day showed rather less pus, but a very large number of bacteria.

Cultures from this case showed the staphylococcus pyogenes albus in pure culture.

Case X.—Mrs. R. F., female, aged 20, native of the United States, admitted to Hospital January 2nd, 1895, complaining of typhoid fever.

The family history is negative.

She has had the usual children's diseases; married two years; one child, living and well.

The patient went to bed nine days ago, but had not been feeling well for some months previously; was thought to have had malaria;

had headache, diarrhœa, pain in the back. She has vomited a few times, and had diarrhœa continually after going to bed; she did not have any hæmorrhages previous to admission. She became slightly delirious three days before entrance.

Note on admission: The patient is very dull and apathetic; pulse small, soft and rapid; sordes on lips and teeth. She can be made to answer questions with greatest difficulty, and then answers only in monosyllables. The lungs are clear, except for a few fine râles at the bases. The heart sounds are rapid, but clear. A number of spots on the abdomen suggest faded rose-spots.

Patient had a hæmorrhage from the bowels, gradually sank, and died within forty-eight hours of admission.

Temperature on admission was 105.6°; fell, reaching 102° six hours after admission, and from then until death it ranged between 101° and 103°. It was 103° at the time of death.

The urine was highly albuminous, but no pus was noted until the day of death, when many pus cells were present. It contained a large number of granular, waxy and hyaline casts, all of which were bile-stained.

Autopsy.—Anatomical Diagnosis.—Extensive ulceration in small and large intestines; hæmorrhagic infiltration of ulcers.

Beginning 288 cm. above the valve is the first ulcer; the central part is sloughing and hæmorrhagic. From this point downwards the ulcers increase in size and extent; sloughs are still adherent to many of them; in others they have separated, exposing the circular muscular coat. In general, the ulcers show an hæmorrhagic appearance. Just above the valve is a very large, irregular, hæmorrhagic ulcer, partly covered by slough and partly clean. The cæcum presented many small follicular ulcers, and similar ones occurred throughout the ascending and transverse colon. Many of the swollen follicles presented necrotic tops. The edges of the ulcers were usually hæmorrhagic. In the descending colon and rectum the ulceration was more advanced, and the edges of the ulcers very hæmorrhagic. The mesenteric glands were much swollen. The spleen was enlarged —weighed 475 grammes. The kidneys were swollen and pale. The heart was normal; muscle firm.

Cultures from the urine in this case showed both the colon and the typhoid bacillus.

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V.—CERTAIN FORMS OF INFECTION IN TYPHOID FEVER.

BY SIMON FLEXNER, M. D.

(*From the Pathological Laboratory of the Johns Hopkins University and Hospital.*)

- *A.* **Typhoid septicæmia associated with focal abscesses in the kidneys due to the typhoid bacillus.**
- *B.* **General Infection with the typhoid bacillus; perforative peritonitis caused by the streptococcus pyogenes.**
- *C.* **Typhoid Fever associated with miliary abscesses in the kidneys due to the typhoid bacillus. Non-transference of typhoid bacilli from mother to fœtus.**
- *D.* **Typhoid Fever with perforation of the intestine; acute peritonitis with bacterial poly-infection.**
- *E.* **Typhoid Fever with perforation of the intestine (3rd week of the disease); acute streptococcus peritonitis and streptococcus septicæmia; absence of typhoid bacilli from cultures.**
- *F.* **Typhoid Fever; death from hæmorrhage (6th week of the disease). Disappearance of typhoid bacilli. Infection with bacillus coli communis.**

The distribution of the typhoid bacilli in the body in typhoid fever must be considered as still presenting interesting features. That the bacilli may be present in the blood of these patients seems, in view of certain observations (Karlinski, Vincent), very probable, although the work of the earlier investigators (Rütimeyer, Almquist, Pasquale, Guarnieri, Neuhaus), who claimed to have cultivated the organism from the general blood and that of the rose-spots during life, has, through later studies (Janowski, Stagnetto, Grawitz, Fränkel and Simmonds, Sittman), been discredited. It is, however, significant that the observations in which typhoid bacilli were believed to have been cultivated from the blood during life, and again at autopsy, as in the case of Karlinski, date from a time when the means of distinguishing between these organisms and certain other bacterial varieties, much resembling them, were not so complete as now.

It is a well-known fact that all cases of typhoid fever do not complete their course as a simple infection, by which is meant that the morbid process, from its inception to its close, is due entirely to the action of the typhoid bacillus. The possibility of the interaction of other micro-organisms, secondary invaders, is now not to be doubted, although the effects of these subsidiary organisms may be comparatively slight, and entirely limited to the intestinal tract. It must always be a matter of importance—the question as to just what part of the intestinal lesions are caused by the typhoid bacillus acting alone, and how much of these are attributable to other micro-organisms, chief among which are the pathogenic staphylo- and streptococci. There are instances, however, in which the secondary micro-organisms come to play a more active part, as are seen in cases of metastatic abscess formation and inflammation due to the pyogenic bacteria (spleen, mesenteric glands, heart valves), the portal of entry into the system doubtless being the ulcerated intestinal tract; and in cases of perforative peritonitis the importance and significance of these organisms are hardly to be overestimated.

Among the fatal cases of typhoid fever which have come to autopsy in the Hospital, those here given have been chosen on account of their possession of features which lend interest to them in connection, first, with the distribution of the typhoid bacilli in the body and the unusual localized lesions directly attributable to them, and, second, the nature, distribution and effects of the secondarily invading bacteria.

CASE I.—*Typhoid Septicœmia associated with focal abscesses in the kidneys, due to the Typhoid bacillus.**

In individuals who have died of typhoid fever, provided death has occurred not too late in the course of the disease, it is usually possible to cultivate the typhoid bacillus from various organs, among which the mesenteric glands, spleen, liver and kidneys (not to refer to the intestines) may be mentioned. The experience of this laboratory indicates that the bile is particularly rich in the typhoid organisms, and the autopsy records of the Hospital contain many instances in which they have been isolated from this fluid in pure culture. Now that Quincke and Stahlen have directed attention to it, the bone-marrow will doubtless be found to be a common habitat of the organisms in the disease; and in several recent autopsies I have found them in considerable numbers in this situation. In cases of abortion they have been found in a conclusive number of cases to have passed through the placental barrier (Widal and Chantemesse, Hildebrand, Eberth, Ernst, Janizewski, Frascani), and to be present in the organs and even in the blood of the fœtus.

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* This case, including plates and bibliography, appeared in the *Journal of Pathology and Bacteriology*, April, 1895.

The bacillus of typhoid fever is, therefore, distributed in such a way as to indicate that it has, at some time during the disease, been present in the blood current. Yet it must be remembered that it is not, unless most exceptionally, found in the blood outside of organs, even at autopsies. The rarity of this condition is sufficient apology for recording cases in which a general typhoid infection of the body existed at autopsy.

This case presents, in addition, another feature which is perhaps of interest. The recent contributions to the study of the relation of the typhoid bacillus to local foci of suppuration have tended to show that in a variety of inflammatory processes this organism alone is concerned. This view, first advanced by A. Fraenkel, has, as is well known, been vigorously contested by Baumgarten and E. Fraenkel. The latter have contended that other bacteria, particularly the pyogenic cocci, were present, along with the typhoid bacillus, and were overlooked or had died out at the time of the examination. Now in the kidneys in this case a number of abscesses existed in which no other micro-organisms than the typhoid bacilli were demonstrable. Any assumption that other bacteria had been present is not to be reconciled with the short duration of the illness; and the numbers and relation of the typhoid bacilli to the foci of suppuration leave no doubt of their action.

The clinical course of the case was unusual. I am enabled, through the kindness of Dr. Osler, to whose ward the patient had been admitted, to give an abstract of the clinical history.

CLINICAL SUMMARY.—*Illness of two weeks' duration before admission; moderate fever; enlarged spleen; rigidity of muscles of neck and of right arm; mental dulness and delirium; cutaneous hyperæsthesia and increase of the reflexes; small amount of albumin, with red blood corpuscles in the urine; no diazo-reaction; for 3 days before death normal temperature; parotitis.*

Susan B., æt. 18, colored; admitted to the medical wards, 23rd April, 1894, complaining of headache, pains in the abdomen, and general weakness.

The patient is an only child; her father is living, her mother is dead, but from what disease could not be learned. There is a history of tuberculosis in the father's family.

She does not remember ever having had any of the diseases of childhood; was always strong and well; menstruated first at 17, and has been regular. Five weeks ago she began to have sick headaches, but without vomiting. She kept at work, though feeling wretched, until 2 weeks ago, when she began to have pains in different parts of the body, and weakness. She was restless and feverish, without appetite, slept very badly, and had diarrhœa. The patient was so dull and stupid that it was only with difficulty that a history could be obtained.

On admission at 5 p. m. her temperature was 103.7°; the pulse 120, soft and regular. She vomited a dark greenish material. That night she was restless, but the temperature did not rise above 103.5°. She was sponged, and whisky was administered. The urine obtained and examined on the evening of admission was slightly brownish in color, acid; specific gravity, 1010; it contained a small amount of albumin, and microscopically showed leucocytes and red blood cells. No casts were seen; the diazo-reaction was not present.

24th April.—The patient is a small, thin, poorly nourished girl, and looks as if she had been ill some time. She lies on her back with the eyes half closed, and the face has a dull, typhoidal expression. The temperature was 102.6° at 8 o'clock; the pulse was 116, regular. The abdomen is not distended, but is held rather tense. The spleen is palpable, fully 4 cm. below the costal margin. During the examination the patient complains much of tenderness everywhere. The examination of the lungs and heart showed nothing abnormal. The first sound at the apex was a little prolonged and dull. The patient had one stool since admission, which was small, firm, and somewhat clay-colored.

25th April.—The patient had a better night; the temperature for the greater part of the last 24 hours has been below 102°. The urine is dark amber-colored, acid in reaction; specific gravity, 1010; no diazo-reaction; a small amount of albumin; contains leucocytes and a small number of red blood corpuscles. The patient had one movement to-day, in which there was a small fæcal concretion, concentrically laminated. She had through the day a good deal of vomiting, and she took her nourishment—milk and albumen water—very badly.

26th April.—Patient has vomited less; temperature has not reached 102°; no movement from the bowels; pulse is feeble, and ranges from 112 to 120. Only 400 cc. of urine was collected; she passed some involuntarily. Towards the afternoon of the 26th it was noticed that the head was much retracted, and held very stiffly, and the right arm was in a condition of extension, somewhat rigid, and any attempt to flex it caused pain.

27th April.—The temperature to-day was lower, and at 6 a. m. reached 98.9°, and the highest throughout the day was 100.6° at 6 p. m. She vomited repeatedly, talked incoherently, and moaned a great deal. She had one small stool at 10 p. m. She seemed very sensitive to the slightest touch. The retraction of the head and the rigidity of the arm persisted.

It did not seem possible to decide as to the nature of the case. Though it looked more like typhoid fever on her admission, the retraction of the head and rigidity of the neck muscles, the general sensitiveness and the rigid extension of the right arm suggested, very naturally, cerebro-spinal meningitis. The blood was carefully examined for malarial organisms, and cover-slips were stained for tubercle bacilli; the leucocytes numbered 6,000 to the cubic millimetre. The urine was yellow, acid, distinctly cloudy, with heat and nitric acid; no diazo-reaction. Microscopically there were many epithelial cells, chiefly from the bladder, some leucocytes, and a smaller number of blood cells. The sediment was collected and stained for tubercle bacilli with negative result.

28th April.—On account of the vomiting she has been fed, for the past 24 hours, by rectal injections. At the morning visit she was lying with the head thrown back, and resisted slightly any attempt to bend the neck. She replies to questions in a confused and hesitating manner. There is no photophobia; the pupils are equal and react to light. After being aroused, she lies with her eyes open, but with rather a staring expression. She moves the left arm readily, but the right is extended and motionless by her side. It is not so rigid to-day, though she winces and cries out when any attempts are made to flex it. The deep reflexes in the left arm are active; in the right they cannot be tested. The knee jerks are a little exaggerated, and there is well-marked ankle clonus on both sides. The abdomen is not swollen; not especially tender. As satisfactory an examination as possible was made of the uterus, but nothing abnormal could be detected. The temperature fell to 98.2° this morning, and the highest registered through the day was 100.1°. The patient had one well-formed stool.

29th April.—The rigidity of the muscles of the neck is still marked, and the stiffness in the right arm persists. Mentally she seems somewhat clearer, says she has no headache, and puts out her tongue when asked. From 10 o'clock last night the temperature has been a little below 99°. She has been passing urine involuntarily.

30th April.—The temperature continues normal; was 98.2° at 8 p. m. and 98.4° at 8 this morning. The pulse is feebler, just 100, and not irregular. There is no strabismus. She moves the left arm about freely; the right arm shows slight clonic movements, and at intervals becomes quite rigid. The ankle clonus could not be obtained to-day. The abdomen is flat, and not more sensitive than in other parts.

May 1st.—Until 8 a. m. the temperature was about 99°. This morning it was noticed for the first time that there was a soft swelling in the left parotid region, which is not painful. The vomiting has been very obstinate. She retains the nutritive enemata. To-day the right arm is easily flexed, and can be moved in all directions. The heart sounds are, and have been, perfectly clear. There are few râles at the bases of the lungs, but there has been no diffuse bronchitis. The temperature rose a little through the day, and reached 100.2°; the pulse became more rapid and feeble, and she died at 5.30.

Autopsy 17 hours after death.

ANATOMICAL DIAGNOSIS.—*Typhoid fever (ileo-typhus and colo-typhus); hæmorrhagic enteritis; acute splenic tumor; multiple abscesses in the kidneys; parenchymatous degeneration of the liver and kidneys; purulent infiltration of the parotid gland; œdema of lungs and glottis.*

Body of a small, sparely-built negro girl. Subcutaneous fat in small amount. Muscles bright red in color.

Peritoneal cavity.—No excess of fluid. The intestines are distended.

Pleural cavities.—Both dry. The lungs are free from adhesions. Both are voluminous.

Pericardial cavity.—No excess of fluid, and both layers of the pericardium are smooth.

Heart.—Right auricle and ventricle contain dark and partly decolorized clots. In the left ventricle a small, partially decolorized clot. All the valves are normal.

Lungs (Right).—The upper and middle lobes are œdematous; the lower lobe is congested. The bronchi are filled with frothy serum. Vessels at base free. (Left).—Lower lobe congested; the upper lobe œdematous. Bronchi contain frothy serum; vessels at base free.

Liver.—Weight, 1700 grms. It is soft, swollen, and the sharp edges are rounded. On section it is fatty in appearance, the lobular markings being obscure. The bile is thin, light-colored, and contains a granular sediment.

Spleen.—Weight, 420 grms. The capsule is thin and distended. On section the substance is soft and pulpy; the follicles are visible and apparently not enlarged.

Mesenteric glands.—Swollen and congested.

Adrenal glands.—Apparently normal.

Kidneys.—They together weigh 320 grms. (Left).—Large and pale. The capsule strips off easily, and beneath it, imbedded in the cortex, a number of small white nodules, larger than miliary tubercles, can be seen. Others are visible in the cut sections of the kidney. (Right).—In general the same as the left. In this kidney there are several larger white areas, the largest of which is triangular in shape; the base of the triangle, measuring 4 mm., is situated at the surface. The capsule corresponding with this area contains small hæmorrhages.

Parotid gland.—On the left side it is swollen and infiltrated with pus.

Larynx.—The posterior epiglottic tissues and the aryteno-epiglottidean folds are infiltrated with serum, and present a gelatinous appearance.

Intestines.—The small intestine is bile-stained throughout. The mucous membrane is cloudy, and sticky mucus covers its surface. The patches of Peyer in the upper parts of the small intestine present the shaven-beard appearance. The first ulceration occurs in the ileum 200 cc. above the valve. It is round, about the size of a 1-cent piece, and is superficial and clean. 160 cm. above the valve there is a large ulcer, involving the entire circumference of the gut; it is 10 cm. in width, is irregularly convoluted superficially, and the surface is necrotic and sloughy-looking. This ulceration apparently does not reach beneath the submucosa, but the whole thickness of the intestine is involved in the infiltration. On the serous surface small white points (lymphomata) can be seen. Between this ulceration and the ileo-cæcal valve there are several smaller losses of substance. The lower end of the ileum is, together with the valve, inclosed in one larger ulceration of the same general appearance as the larger ulcer already described. Some of the solitary follicles of the cæcum are ulcerated, others are swollen, the centres of these often being necrotic. The ascending, transverse, and in part the descending colon, show the same conditions as the cæcum.

Beginning at the larger ulcer, 160 cm. above the valve, and continuing downwards to the latter, the mucous membrane is infiltrated with blood, the surfaces of the valvulæ conniventes being more affected than other places, except immediately about the ulcers. The swollen and ulcerated follicles in the large intestine are surrounded by a zone of hæmorrhage.

Fresh frozen sections of the heart muscle show it to be free from fat; sections of the liver and kidneys show parenchymatous and fatty degeneration of the epithelial elements of these organs.

Bacteriological examination.—Cover-slip preparations made at the time of the autopsy from bile, spleen, and nodule in the kidneys, showed many bacilli having the form and staining properties of the typhoid bacillus. This organism was found alone in these cover-slips. From the pus of the parotid gland the cover-slip preparations showed many streptococci.

Cultures.—Agar-agar plates were made at the autopsy from the heart's blood (right auricle), lungs, kidneys, mesenteric glands, spleen, bile, liver, bone-marrow (femur), and parotid gland. These plates, kept at 37° C. for 48 hours, gave the following results:—

Bile.—Crowded with colonies, apparently all of the same kind. Proven to be a pure growth of the typhoid bacillus.

Spleen, mesenteric glands, and bone-marrow, all contained many colonies of the typhoid bacillus.

Kidney.—Two cultures were made from this organ. The first was taken from one of the white nodules, the second from the intervening kidney substance. From the nodule many colonies developed, and they consisted entirely of the typhoid bacillus. The other plate contained fewer colonies, from which two kinds of organisms were separated, one agreeing with the typhoid bacillus, the other with the Bacillus coli communis.

Lungs.—From the congested portion of the right lower lobe three organisms were isolated—(1) Streptococcus pyogenes; (2) Typhoid bacillus; (3) Bacillus coli communis.

The streptococcus colonies predominated.

Heart's blood.—On this plate 20 to 30 colonies, all having the same features and proving to be the typhoid bacillus, developed.

Parotid gland.—The agar-agar plate was crowded with minute colonies of the Streptococcus pyogenes. Sections of the gland hardened in alcohol showed a pure streptococcus invasion along the ducts into the gland acini, associated with an interstitial and parenchymatous infiltration of leucocytes, with polymorphous nuclei.

In studying the bacilli isolated from this case, special attention was paid to distinguishing between the typhoid and the colon bacillus when they occurred together (lungs and kidneys), and to proving that the organisms found in the heart's blood, kidney nodules, as well as in the other organs mentioned, were really typhoid bacilli.*

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* The recent writers on the means of distinguishing the typhoid and colon bacilli regard the fermentation (Smith, Chantemesse and Widal, Fuller, Dunbar, Welch, Valentini, Germano and Murea, Silvestrini), milk (Dunbar, Maloz, Valentini, Welch, Blachstein, Silvestrini), and indol (Péré, Ferrati), tests as sufficing to establish this distinction, and my own experience accords with that of these authors. Recently a new medium has been introduced by Wurtz for separating these two forms. It consists of lactose-gelatine colored with an alkaline litmus tincture. The colony growth in this medium can, through the change in the reaction produced in it, be used for this purpose. The colon bacillus colonies are said to become pink, whereas the typhoid remain blue. In several tests recently made with this medium, agar being used in place of gelatine, I found that the typhoid bacilli produced sufficient acid when acting upon lactose to turn the medium slightly pink; but the acid-reaction is less strongly marked than that caused by the colon bacillus. I have, moreover, had the opportunity of observing a variety of the typhoid organism which, when planted in litmus milk, gives at first a typical reaction; that is, after 24 to 48 hours at 37° C., it causes a faint pink color to appear. This color persists for some days (5 or 6 in the thermostat), when it changes back to blue, the blue gradually increasing in intensity until after 10 days or 2 weeks, the alkaline-reac-

The weight of opinion among bacteriologists at this time, is that the colon group of organisms can be sharply differentiated from the typhoid bacillus. However, it no longer suffices for distinguishing them to observe the colony growth upon agar and gelatine plates, or the growth upon potato; neither does the possession of motility and stainable flagella serve to distinguish the typhoid from the colon bacillus. On the other hand, the power of acid and indol-production, the property of setting up fermentative changes in sugar with the liberation of gas, and the coagulating influence upon milk, possessed by the colon group of organisms, separate it from the typhoid organism, which produces alkali, does not yield indol in cultures, is not capable of fermenting sugar, and has no coagulating effect upon milk.

The bacilli separated from this case were tested by these means, by observations of their growth upon different solid culture media, as well as by microscopical study; and it was found that in the heart's blood, spleen, bile, liver, mesenteric glands, bone-marrow, and abscesses of the kidneys, the typhoid bacillus was present in pure cultures.*

The number of observations at the present time referring to the typhoid bacillus as the cause of post-typhoid inflammations is so large as to admit of little doubt of an etiological connection between the

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tion is very prominent. This fact agrees with Wurtz's observations on the alkaline (ammonia) producing power of the typhoid bacillus, as opposed to the acid production of the colon bacillus. Pfeiffer has, moreover, just pointed out that animals rendered immune from the typhoid bacilli, contain an anti-toxine in their blood which is bactericidal to them, and not to the colon group of organisms, and other forms which seem to be even more closely related to the typhoid bacillus.

* The typhoid bacillus has been found in local inflammations as follows:—In connection with bone giving rise to osteomyelitis and periostitis. by Ebermaier, Orlow, Valentini, Achalme, Chantemesse, Colzi, Melchoir, Dupraz, Buschke, Sultan; in abscesses of skin and muscle and periarticular abscesses, by Melchoir, Raymond, Rosin and Hirschel, and Swiezynski; in acute endocarditis, by Carbone, Vincent, Girode; in circumscribed peritonitis, by A. Fränkel, Lehman; in cerebro-spinal meningitis, by Kamen, Honl, Hintze, Stübler, Mensi and Carbone, Vincent; in abscesses in the spleen and mesenteric glands, by Roux and Vinay, Lehman, Flexner; in purulent cholecystitis, Gilbert and Girode Chiari; in sero-fibrinous pleurisy and empyema, by Ferret, Loriga and Pensuti, Valentini, Spirig, Weintraud; in purulent strumitis, by Colzi, Honl, Jeansalme; in suppurative epididymitis, by Gilbert and Girode; in suppurative orchitis, by Tavel; and in a suppurating lipoma of the knee, by Sittman.

organism and the pathological process. The length of time during which this organism can remain in the body is not a little surprising. Among the first of the observations bearing on this point, is that of Welch, who found in a rabbit which had been inoculated with typhoid bacilli 4 months previously, and had recovered, and which later succumbed to another experiment, that the typhoid bacilli which had disappeared from all other situations were still present in considerable numbers in the bile of the animal. The longest period yet recorded in which the typhoid bacillus had been found in the body after recovery from a typhoid fever, is that reported by D. Buschke, in which, in a rib-abscess, they were present seven years after. The list of cases in which this organism has been found in local foci of suppuration is now very large, and includes most situations in the body. In the study of some of these it is not improbable that the strict bacteriological requirements, concerning, in the first place, the identity of the bacillus, and in the second the absence of other organisms, may not have been carried out. But a few carefully studied cases, in which the typhoid bacillus is proven to have been present alone, renders the doubtful ones more probable. In the study of the abscesses in the kidneys* in this case, this fact was kept in mind. Therefore, examinations were made—(1) of cover-slip preparations from the abscesses, (2) of cultures in agar-agar, etc., (3) sections from the kidney hardened in alcohol were stained in various ways, as will appear, for organisms, with the result that the typhoid bacillus was found alone in the lesions.

The abscesses can be separated into two groups, depending upon their sizes. The smaller ones are limited to the cortex of the kidney.

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*The typhoid bacillus has been found in the kidney by the culture method in many instances, in which no lesions have been detected, and in association with lymphomata by several authors, viz., Konjajeff, Spirig, Karlinski. Faulhaber was able to grow from an anæmic infarction of the kidney, in a case of typhoid fever associated with fresh vegetations on the mitral valve, a large number of typhoid colonies. The lymphomata are described as usually microscopic in size, but they may reach a size sufficiently large to be seen with the unaided eye. They are composed of accumulations of round cells with single nuclei. The bacilli are present, so far as they can be seen, in small masses and groups, lying amid the cellular infiltrations. Konjajeff saw them in both capillaries and tubules, while Spirig could not clearly ascertain their situation. Neither discovered them in the glomeruli. Von Wunschheim has just published a report of 2 cases, in which abscesses in the kidneys were produced by the typhoid bacillus.

Their shape, as found upon microscopical examination, is linear rather than round, the central zone richly infiltrated with pus cells, being surrounded by a wide but less thick, round-cell infiltration. Specimens stained for 2 hours in Loeffler's methylene blue, differentiated in 1-1000 acetic acid, dehydrated in absolute alcohol, and cleared in oil of cloves, show, under a low power,—objective No. 3, ocular No. 3,—large masses of bacteria; in a single section as many as six of these collections of bacteria may be visible. These masses of bacilli are entirely and promptly decolorized by Gram's method of staining, and no other organism could be found, after painstaking search, in specimens stained in this manner. The same result was obtained with Weigert's fibrin stain.

Towards the centre of such an area the cellular infiltration is so great as to obscure the structure of the tissues; and when the latter can be made out the staining is feeble, and in it many nuclear fragments are to be seen. The infiltrating cells vary in form, some of them possessing single and others compound (polymorphous) nuclei. At the edge of the infiltration it can be readily seen that many of the cells are intertubular. These partake as a rule, although not exclusively, of the character of small round cells. Some of the tubules are dilated and filled with polyform leucocytes. The masses of bacteria are often so surrounded by cells that their location is not always to be made out with certainty. But they appear at times to be intratubular; besides the large masses described, smaller foci of bacterial accumulation are to be seen among the cells.

The larger abscesses involve the medullary as well as the cortical part of the organ. From the surface the infiltration extends in somewhat irregular parallel lines for a considerable depth into the pyramids. In such an area the nuclei of the cells are to a large extent of the polyform (polynuclear) variety. However, between the tubules, at a little distance from the thickest infiltration, there are many small cells with spherical nuclei present. In the central foci of leucocytic infiltration the kidney tubules are dilated and filled with pus cells. Tubules of the convoluted type are often distended to more than twice their normal size, and the straight tubules of the medullary rays are equally affected. Following the tubules downward into the pyramid, the intratubular exudate is very common, while the intertubular is more scanty.

The bacteria are in large masses and in smaller aggregations, and may now be seen to be distinctly inside of the tubules and surrounded by pus cells. Indeed, some cells appear to have taken up the bacteria. The forms of the bacteria are readily made out in the smaller accumulations. They consist of short, plump rods, with rounded ends, which in the alkaline methylene-blue fluid show an irregularity of staining. The larger masses can be easily seen with a No. 3 objective (ocular No. 3), whereas the smaller groups require the aid of the one-twelfth in. oil immersion to bring them to light. A few small groups of bacteria were observed between the tubules, probably intravascular.

An interesting feature was observed in several glomeruli in infiltrated areas. Masses or thrombi of bacteria were seen in the afferent vessels, and similar bacilli were present in the glomerular capillaries, and had passed through these, as they were found again in numbers in the capillary space. The epithelium lining the capsule of Bowman was in such cases entirely degenerated.

The epithelium of the cortical tubules, particularly of the convoluted portions, is swollen, granular, and often degenerated. Those tubules, which are adjacent to, or within, the areas of cellular infiltration, show at times an absence of stainable nuclei in the lining cells. The form of epithelial degeneration, which is seen most frequently, is, however, of the hyaline variety, and the hyaline material, which is highly refractive, can be seen to run together to form actual tube casts. Those tubules, in which many pus cells occur, have no demonstrable epithelium, or are lined by low, compressed cells, often still possessing stainable nuclei.

So far as these foci are concerned, the process is not distinguishable from acute suppuration, although the tissues show no particular tendency to soften and break down.

It should be mentioned that in a few places there are considerable masses of bacteria inside of tubules, showing less reaction around them, on the part of the tissues, than that described. Such appearances are uncommon in the cortex, but in the pyramids, in the collecting tubules, masses of bacilli are embedded in pus cells, with little or no surrounding intertubular infiltration.

There can be no doubt that the bacilli gained entrance into the tubules through the glomerular capillaries. This is shown not only by the appearances already described, but also by the almost complete absence of the bacilli in the intertubular tissue. It would appear that most of the pus cells seen in the pyramidal tubules also come from places higher up in the kidney.

The size of the masses of bacteria in some of the pyramidal tubules suggests that an increase must have taken place after these parts were reached. In a few instances a tubule, usually in the papillary portion of the pyramid, has been completely filled by a growth of the bacilli, and around these there may be no reaction whatever, so that a post-mortem increase is not to be excluded.*

In considering the features presented by this case in the light of the literature bearing on the typhoid bacillus, it would seem as if it were necessary to regard this organism as being concerned in a variety of pathological conditions. Just as a larger and fuller acquaintance with the properties of the diplococcus pneumoniæ has shown it to be at one time able to cause as definite a pathological process as acute lobar pneumonia, at another abscess formation, and at still another a general infection of the body, so the typhoid bacillus seems capable of producing on the one hand the typical lesions and classical features of typhoid fever, and on the other of localized foci of inflammation and suppuration, and finally a genuine typhoid septicæmia.

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* A few cases of especial interest have been reported in which the typhoid bacillus has been widely distributed in the body in association with definite lesions, or in which this organism has been isolated from the organs at autopsy with very slight or even entire absence of lesions in the intestine indicative of typhoid fever. It is at this time becoming to be very circumspect in the interpretation placed upon these cases, unless the most rigid requirements as to the identity of the organism are carried out. Hence in the cases reported by Banti and Karlinski of a typical typhoid fever, where no definite lesions of typhoid fever existed, and yet the organisms were obtained from the blood during life, and the organs after death, it may be questioned whether they are to be accepted as conclusive. But the same is not true of the case reported by Du Cazal in which, upon the closest inspection, no lesion could be found in the intestine. Yet typhoid bacilli which behaved in a typical manner upon various culture media, and did not ferment lactose nor redden Wurtz's agar, were isolated from the much enlarged spleen. The symptoms during life were those of typhoid fever, and at the autopsy the mesenteric glands, spleen and kidneys were swollen and congested. The case of Vincent contained a number of superficial ulcers in the ileum, and a deeper one just at the valve. The spleen was swollen, and in it was an abscess the size of a walnut, containing thick, viscous, white pus; the mitral valve contained several fresh vegetations; there was a hæmorrhagic infiltrated placque, the size of a 5-cent piece, at the summit of the left ascending parietal convolution, and from all these typhoid bacilli in numbers were obtained in pure culture. They were also grown from other organs and the heart's blood. The bacilli were decolorized by Gram's method, and grew like typical typhoid bacilli in bouillon, Vincent's (carbolic acid) bouillon, and upon agar-agar.

It would be interesting if not profitable to inquire into the peculiar conditions which permit at one time the invasion of the blood by this organism, whereas, as a rule, it does not find in it a suitable medium for development. The fact is too well known to need repetition, that normal human blood serum quickly kills many typhoid bacilli. It is not improbable, therefore, that in such instances the germicidal power of the blood has been either annihilated or diminished, and it may be well to ask whether, as in the experiments of Vincent and Chantemesse and Widal with the streptococcus and its soluble products, or of Sanarelli with the products of the bacillus coli communis and the bacillus proteus, the general infection might not be explained by the development of a concomitant infection, in this case a streptococcus parotitis. Vincent has shown, moreover, that in human beings a streptococcus invasion of the body makes the prognosis very grave, even when it occurs towards the close of the disease, and after the typhoid bacilli have almost disappeared from the system. Among his cases is one that was complicated by an otitis media of streptococcus origin, in which on the fifteenth day there was augmentation of the fever, and an inverse type of temperature. Seven days later death occurred. The autopsy showed a general streptococcus and typhoid infection, the former organisms predominating in the heart's blood. But as opposed to such a supposition as the above, are the many instances of suppuration due to the pyogenic cocci, in the course of typhoid fever, in which there is an absence of evidence pointing to an invasion of the blood by the typhoid organisms. However, it may be well to study more particularly the relation of the typhoid bacillus to the blood in human beings in this class of cases.

CASE II.—*General infection with the typhoid bacillus; perforative peritonitis caused by the streptococcus pyogenes.*

Barbara W., aged 21, admitted to the medical wards (Dr. Osler) September 5th, 1893, complaining of pain in the neck, chest and abdomen, and great weakness.

Two of her brothers are ill with typhoid fever in ward F, and several other members of the family have had the disease this summer, and she has recently been nursing a brother who died of the disease.

With the exception of pneumonia at thirteen, she has been very healthy.

Present illness began about two weeks ago, with headache and loss of appetite; bowels were constipated, and she had at times slight pain in the abdomen. She had also cough and pains in the chest. She has been keeping up in order to help her mother do the nursing at home.

On admission the temperature was 102.5°, and rose in the evening to 104°. She had retention of urine and was catheterized.

Patient was a healthy looking, well nourished girl; face a little flushed; tongue swollen and furred. The abdomen was everywhere soft; there were no rose-spots; the spleen was not palpable. The examination of the lungs and heart was negative. The temperature range was not high, and during the first three days in the hospital she had only six baths. At first the bowels were constipated; then on the eighth she had four stools.

On the 9th and 10th the temperature was higher and more persistent. The pulse was regular, of good volume, and not dicrotic. The abdomen was not distended; spleen was not palpable, and there were no rose-spots to be seen. She had two or three soft movements a day.

On the 11th and 12th the temperature kept between 103° and 104°. The abdomen was soft, not distended, not painful. The tongue was furred, not dry.

On the 13th she was not so well; pulse was more rapid, reached 130; temperature was nearly 105°. She complained of pain in the abdomen, but there was no special swelling. She had three movements on the 13th.

On the 14th the temperature was almost constantly above 104°, and at 2 a. m. reached 105.2°. The abdomen was slightly distended. The diarrhœa had increased very much; the respirations were short and costal. The hands and feet were cold and clammy. The gravity of the general condition contrasted with the comparatively slight local features. The abdomen was not much distended, and only on deep pressure painful. There was fœtal heart rhythm. Throughout the night of the 14th she became much worse; movements were frequent, and the collapsed condition was marked. She was given subcutaneous injections of salt solution. The pulse was very rapid, and almost uncountable. The patient took her nourishment well. The abdomen became more distended, tympanitic, and tender. There was 3 cm. of liver dulness in the right nipple line. The patient became much worse throughout the day and died at 2 p. m. in the afternoon of the tenth day after her admission to hospital, and about the 21st day of the disease.

Autopsy seventeen hours after death.

ANATOMICAL DIAGNOSIS.—*Typhoid fever; perforation of the appendix vermiformis, with peritonitis due to the streptococcus pyogenes; general infection with the typhoid bacillus.*

Body of a well nourished girl, 162 cm. long; rigor mortis present in the extremities. Abdomen much distended, the tympany extending upwards over the liver.

The peritoneal cavity on incision permits an escape of gas and contains a considerable amount of yellowish brown fluid.

The intestines are matted together by fresh fibrino-purulent exudate, most abundant in the right iliac region. Coils of the small intestine have a dry glazed appearance, and are much distended by gas; the serosa is intensely injected. On separating the ileum from the cæcum, to which it was attached by fresh adhesions, the enlarged and swollen appendix was brought to view. This runs over the right brim of the pelvis. In the appendix, almost at its extremity, there is a perforation leading into its lumen. There is no attempt at localization of the abscess. The diaphragm on the right side is at the third space; on the left side, at the fourth rib.

Intestines.—Throughout the entire ileum and the lower part of the jejunum the solitary glands and the Peyer's patches are uniformly enlarged. As the ileo-cæcal valve is approached the patches of Peyer become much more prominent, and many of these are capped with small yellow sloughs. Beginning about 40 cm. above the valve there are actual ulcerations, none of them, however, being clean. The mucous membrane of the cæcum and the ascending colon is much swollen and congested, the solitary follicles being enlarged, the apices of some capped with sloughs. The vermiform appendix is 9 cm. in length; its mucosa is swollen, and varies from 4 to 5 mm. in thickness. There are large areas of necrosis of the mucous membrane present, and 2 cm. from its tip a perforation occurs, whose diameter is 5 mm.

The mesenteric glands are greatly swollen and congested.

The spleen weighs 280 grammes; the capsule is free from adhesions; on section it presents a purplish-brown color, and it is of very friable consistence.

The liver weighs 1350 grammes; the capsule is smooth; on section the organ is of uniformly yellowish-brown color and friable. The gall bladder contains a very little turbid yellowish-brown bile.

The kidneys are essentially alike. They are somewhat swollen; the surface is smooth; on section it is moist; the cortex is opaque. The glomeruli are visible and red.

The heart weighs 185 grammes; is free from valvular lesions; its muscle is soft, pale, and relaxed.

The lungs are bound by old adhesions to the costal wall. On section they are quite uniformly congested.

The other organs apparently are normal.

Cultures in this case were made from the peritoneal cavity, the heart's blood, the bile, and all organs upon agar-agar. From all the sources, including the heart's blood, a growth was obtained which was proven to be the typhoid bacillus. In the peritoneal cavity, cultures of which were made from the purulent exudate, the only organism found was the streptococcus pyogenes.

CASE III.—*Typhoid fever associated with miliary abscesses in the kidneys due to the typhoid bacillus. Non-transference of typhoid bacilli from mother to fœtus.*

Clinical history.—Anne M., æt. 23, white, admitted to the medical wards (Dr. Osler) 14th of January, 1892, complaining of fever and general malaise.

The patient stated that her father, mother, brothers and sisters were all drowned. Previous to the drowning she had lost neither brother nor sister; they had always been healthy.

She has always been healthy, this being her first illness. Catamenia began at 15; married at 18. She had one child, now 2 years old, which is healthy.

Her present illness began five days ago with "quickening movements." Her catamenia have been absent five months. For the last five days she has complained of fever; appetite poor; bowels constipated. She suffered at times from pain in the back.

At the time of admission she was very feverish, skin hot and dry, pulse 120. The spleen was just palpable, and several rose-spots were present over the abdomen. The uterus reached nearly to the umbilicus. The temperature was 105° F. on entrance, and on January 15th it fluctuated between 101.6° and 104.3° F. The patient has been sponged every three hours since her admission, and to-day (January 15th) she looks distinctly brighter.

January 15th.—Patient is well nourished, lips and mucous membranes of good color, tongue dry and brown. Sordes on the lips. Pulse, 24 to the quarter, of distinctly better quality than on entrance, though the tension is rather low. There is a marked dulness of both corneæ, and the upper incisors show the Hutchinsonian nicking distinctly. Thorax.—Respiration and resonance clear in front; in the back an occasional moist, hoarse râle is heard. Heart.—Apex in 4th space, outside nipple. Dulness does not pass 3rd interspace. At the apex the 1st sound is followed by a soft, blowing murmur which is heard a short distance into axilla, over the whole cardiac area, and loudest in the pulmonic region. Heart's action regular. The 2nd pulmonic rather sharp. The mammæ are enlarged, areolæ of nipples dark in color, follicles prominent. Hepatic flatness at 6th rib in mammary line reaches to costal margin; border of liver not palpable. Splenic dulness markedly increased, beginning at 7th rib and reaching nearly to costal margin. The border, which could be just felt yesterday, not palpable to-day, owing to abdominal resistance. Abdomen evenly distended over the lower portion. There is pigmentation about the umbilicus and linea alba. A smooth, rounded, fluctuating mass can be felt extending from the pelvis within one inch of the umbilicus. This tumor is regarded as the pregnant uterus. There are typical rose-spots over the abdomen and chest. On the left ulna, near the elbow-joint, there is a slight prominence. The right tibia is fairly smooth; the left shows a slight prominence at about the junction of the lower and middle third. Urine.—Amber, hazy, reaction amphoteric; sp. gr. 1010; no albumen; distinct diazo-reaction; no sugar. Microscopical examination.—Triple and amorphous phosphates, leucocytes and epithelial cells.

January 19th.—Urine dark brownish-red in color; flocculent deposit; sp. gr. 1018; distinct diazo-reaction; distinct trace of albumen; epithelial cells and leucocytes in sediment; no casts seen.

January 21st.—From the 15th to the 19th the temperature of the patient remained very high, touching every day points above 104° F. Yesterday the highest point reached was 102° F.; this morning it is 101.7° F. Mental condition clear; tendency to constipation rather than to diarrhœa. The pulse is regular, 26 to the quarter and of fairly good quality.

January 22nd.—Urine—no albumen, no casts, distinct diazo-reaction.

January 27th.—Diazo-reaction still present. Color of the urine reddish-brown; neither albumen nor casts present.

January 30th.—Temperature from 21st to 24th remained about the same—touching 104° F. every day; from 24th to 27th the temperature was somewhat lower and the patient seemed rather easier. Yesterday at 10 a. m. temperature reached 105° F. Pulse more rapid and the patient complains of pain in the right breast where a slight caking can be felt in the middle of the gland. This morning the temperature fluctuated between 100° and 100.4° F. a fall of 4.6° F. having occurred between 2 p. m. yesterday and 2 a. m. this morning. The rose-spots are fading, tongue still dry and coated, and emaciation is beginning to become evident. The pulse is 28 to ¼ and of distinctly better quality than for the last two days.

February 4th.—In the last five days the temperature has varied between 98° and 104.6° F. The quality of the pulse seems no worse; this morning it is 29 to the quarter. The urine was examined several times since the last report, the diazo-reaction having gradually grown fainter at each examination, to be missed on the 4th inst.

February 9th.—Since the 4th the temperature has ranged between 99.8° and 104.6° F. The pulse has been more rapid and rather smaller in volume. Wednesday a fresh crop of rose-spots appeared on the abdomen.

February 11 and 12.—The diazo-reaction began to appear again in the urine.

February 13th.—For the last four days the temperature has touched a point above 104° F. daily; pulse 120–140, perfectly regular, though the volume is low. The rose-spots, which lately appeared, are now almost gone. The fœtal movements are lively.

February 15th, 16th and 18th.—The condition of the patient remains about the same. The temperature continues to rise to 104° and over. On the 16th a fresh crop of rose-spots appeared. Pulse on the 15th ranged from 132 to 150.

February 19th.—A number of small boils, quite superficial, appeared on the arm, axilla and back. The patient has been wandering slightly in her mind.

February 22nd.—The fœtal heart was for the first time audible.

February 23rd.—Since 10 p. m., the 21st, the temperature has not touched a point beyond 100.8° F.; the pulse has been slower, and the general appearance of the patient is better. Last night she was quite restless. Urine dark in color, turbid, acid, sp. gr. 1012, considerable albumen, hyaline casts covered with leucocytes, some red blood corpuscles and many leucocytes.

February 25th.—Yesterday morning the patient became considerably hoarser, she could not speak above a whisper, and at noon there was considerable interference with respiration. A considerable degree of œdema was made out about the glottis. Dr. Halsted saw the patient at 8 p. m., and tracheotomy was performed with temporary relief; during the night the patient failed and died at 5.05 this morning.

Autopsy 5 hours post-mortem.

ANATOMICAL DIAGNOSIS.—*Typhoid fever of late date with nearly healed and healing ulcers; ulceration of mucous membrane of the gall bladder; multiple miliary abscesses of kidney due to the typhoid bacillus; furnuculosis of arm and suppuration of axillary gland due to the staphylococcus cereus flavus; œdema glottidis; tracheotomy; bronchitis and broncho-pneumonia. Pregnancy of 6th month; cerebral hæmorrhage and general œdema of fœtus.*

Body of a medium sized, slightly built, somewhat emaciated woman. Surface pale. A tracheotomy wound extends from the thyroid cartilage to within 4 cm. of the sternal notch. On the right arm, near the shoulder several small swellings occur, two or three of which present small external openings which lead into small abscess cavities, containing creamy pus. The corresponding *axillary glands* are enlarged and on incision contain pus. Lymphatic glands of the body generally, not swollen.

Peritoneal Cavity.—Both layers of the serosa are smooth, glistening and moist. The peritoneum covering the small intestine shows a few reddish patches, corresponding to which the serosa is thickened. The mesenteric glands are swollen, dark-red in color and softened.

Small Intestines.—Show many ulcers. These extend from the cæcum to within 2 metres of the pylorus. Commencing at the upper portion of the gut, the ulcers are in general small and superficial, with unclean bases and irregular margins. The large ulcers are circular in outline and their edges are low and covered over with granulation tissue. At the edges of some of these there are smaller areas in which either a new ulceration has taken place, or a part of the old ulcer is left uncovered. Not infrequently a number of ulcers occur close together, these presenting about the same characters. They have clean centres which extend to the muscular coat, the edges being covered over by irregular granulations, or even at times being overlaid by the undermined mucosa (overhanging ulcers). At the ileocæcal valve the area of ulceration is very large, the circular muscle is exposed in the base of the ulcers, many of which have overhanging edges. Those in the higher parts are for the most part nearly healed or rapidly healing, in a few instances, entirely healed, while lower down the healing is far less advanced and fresh ulceration is occasionally met with.

Spleen.—Large, weight 250 grams. The capsule is slightly roughened by small connective tissue outgrowths. Consistence of the organ moderately firm. On section the cut surface is intensely hyperæmic; the Malpighian bodies are visible but not enlarged.

Liver.—Enlarged; weight, 2300 grams. The surface is smooth. On section it is pale, homogeneous and cloudy in appearance. Beneath the capsule of the right lobe there are several small ecchemoses.

Gall bladder.—Distended with bile. The mucous membrane contains several small superficial ulcers and erosions. The ulcers have sharp edges, and they extend apparently no deeper than the mucous membrane. In some the mucosa appears to be advancing over the edge of the ulcers. No concretions present.

Kidneys.—They are both of the same size and general appearance. Together they weigh 400 grams. The capsule strips off readily; the general surface is pale. Imbedded in the kidney substance, just beneath the capsule, numerous greyish foci which can be seen to be composed of light-colored points closely crowded together occur. In addition to these larger single ones are scattered through the cortex. On section the larger collections present somewhat the appearance of infarctions extending into the pyramids. The centres of these are of a greyish color, the periphery being surrounded by a zone of hyperæmia. The cortex of the kidneys is pale, the markings obscure, the regions of the convoluted tubules appearing more opaque than other parts.

Larynx.—The tissues of the epiglottis are infiltrated with serum and present a gelatinous appearance.

Heart.—Weight, 276 grams. All the valves normal. The myocardium pale and easily torn.

Lungs.—In the posterior portion of the lower lobe of the right lung several broncho-pneumonic areas are present, surrounded by œdema. In the left lung there are fewer such foci.

Uterus.—Enlarged. It extends 7 cm. above the symphisis pubis and contains a fœtus and fœtal structures. The fœtus apparently is of the 6th month. It measures 32 cm. in length. No malformation in it was observed. The subcutaneous tissues contain much fluid, and they are pale in color. The serous cavities are filled with clear fluid. The brain substance of the fœtus is softened, and into the left cerebral hemisphere a hæmorrhage has taken place which has much lacerated its substance and extended into the lateral ventricle on that side. The other organs present no noticeable abnormal appearance. They are, however, very soft and œdematous.

Frozen sections.—Sections from the liver, kidney and heart muscle of the mother showed them to be quite fatty. In addition, in the liver, there were many typical "lymphomatous" nodules. The fat in the kidney was situated in the epithelium of the convoluted tubules, but was not present in very large quantity. The secreting cells generally presented a swollen and coarsely granular appearance. The heart on the other hand was very fatty, the fat being distributed diffusely throughout the myocardium.

Bacteriological examination.—This examination consisted in the study of cover-slips and the preparation of Esmarck roll-cultures from all the organs. In addition, in the case of the kidneys, the lesions there were studied in sections of the alcohol-hardened tissues as will appear. *Furthermore a set of Esmarck roll-cultures (in agar-agar) was made from all the organs and the meconium of the fœtus with the uniform result of finding them completely sterile.* Only the results of the bacteriological study will be given here, it being understood that the same methods for the differentiation were used as in the previous case.

Heart's blood and spleen, no growth.

Mesenteric and cæcal lymph glands, liver, bile and kidney, pure cultures of the bacillus of typhoid fever.

Lung (broncho-pneumonic area), pure culture of a streptococcus growing in conglomerate masses without clouding the bouillon.

Pus in axillary gland, pure culture of the staphylococcus cereus flavus.

In the case of the kidney two roll tubes (agar-agar) were made, one from the kidney substance and the other from the greyish-white nodules. In both cases the same organism were obtained, which were shown to be the bacillus typhoideus.

Histological Examination of the Kidneys.—The small foci described are found to be caused by a purulent infiltration of the tissues. The pus cells are present in the interstitial tissue and within the tubules. They are absent from the capsular spaces of glomeruli, even when the surrounding tissue is intensely infiltrated with them and they extend into the pyramidal part of the organ. The tubules in the infiltrated areas show necrosis of their epithelia which at times form consolidated masses within their lumina, the adjacent tubules presenting a hyaline degeneration of their lining cells. The affected cells are filled with hyaline droplets of various sizes which stain with Weigert's fibrin stain. Fibrin filaments are by this method shown to exist in some of the tubules and to be intimately associated with the necrotic cells. The suppuration seems to differ from ordinary suppuration by the less extent of necrosis and the greater amount of hyaline degenerative changes, the tissues, at the same time, not tending to soften and break down. Typhoid bacilli * in considerable numbers are found among the pus cells in the tubules. Other microorganisms could not be demonstrated.

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* In addition to the method given for the demonstration of typhoid bacilli in tissues the following has been employed with excellent results. With it groups of typhoid bacilli, as small as 3 or 4 may be clearly shown among the pus cells, and the fact of their occurrence within pus cells was in this case established. Stain for

CASE IV.—*Typhoid fever with perforation of the intestine; acute peritonitis with bacterial polyinfection.*

Clinical History.—Matthias G., æt. 26, white; admitted to the medical wards (Dr. Osler) August 28, 1891, complaining of headache accompanied by chilly sensations and fever. His present illness began eight days ago.

The patient (German) has been in this country for 9 months; his occupation is that of a carpenter. His father died at 53 probably of pneumonia; mother living. He has two brothers and three sisters living—none dead. He does not know of having had any sickness as a child.

On admission it is noted that he was of large build, that his face was flushed, the tongue thinly furred, the skin dry and hot. Thorax well-formed; clear on percussion and auscultation. Heart sounds clear. Abdomen shows a diffuse erythematous eruption which extends upwards to the lower portion of the chest. A few bright red papules also present which fade on pressure. General tenderness is present over the abdomen, growing more acute in the left iliac fossa. Spleen not palpable. Temperature ranges from 99 to 102.5° F., pulse 88, respiration 24. Blood examination negative.

August 30th.—The spleen is palpable to-day; the urine is of a dark amber color, fairly clear, of acid reaction, does not contain albumen or sugar, and does not give the diazo-reaction. The sediment contains granular casts.

September 2nd.—The temperature has not ranged above 103° F.; the pulse has varied from 90 to 108; respiration 20–24. Fluid clear, abdomen not distended. A few rose-spots over abdomen. Heart and lungs clear.

September 5th.—The spleen is palpable below the ribs; the range of temperature between 99 and 103° F., pulse from 99 to 102.

10 minutes in Stirling's Gentian-violet (Gentian-violet 5 grms., Alcohol 10 cc., Aniline Oil 2 cc., water 88 cc.; filter), place in 1:1000 acetic acid solution for some minutes, dehydrate quickly in 95 per cent. alcohol, transfer to the slide, blot, add oil of cloves to clear and differentiate. Change the oil several times until the desired differentiation is obtained.

September 9th.—Yesterday at 4 p. m. the temperature rose to 104.6° F.; the falls are marked after the bath. Patient was delirious and restless last night. The pulse, in the last twenty-four hours, has been much more rapid; this morning the temperature is 98.2° F., the pulse 118, the respiration 32. At present the patient lies on his back with knees drawn up, his eyes are bright, and pupils dilated. He is delirious and restless. The abdomen is uniformly distended, rather tense and tympanitic. The skin is dry and harsh. Urine turbid, alkaline, pale-yellow in color, gives a faint diazo-reaction, contains many hyaline and granular casts, urates and phosphate crystals.

September 10th.—During the afternoon, yesterday, the pulse became much more rapid (142) and dicrotic. The patient lies in a state of muttering delirium. The urine contains albumen and many casts and red blood corpuscles. The sp. gr. is 1022. The temperature has ranged between 104.2° F. at 8 last night to 95° F. at 6 this morning. The abdomen is considerably distended, very tense and tympanitic; on pressure the patient flinches.

Death at 6.20 a. m. September 11th.

Autopsy five hours post-mortem.

ANATOMICAL DIAGNOSIS.—*Typhoid fever, with clean and deep ulceration; perforation; fibrino-purulent peritonitis. Acute splenic tumor; swelling and softening of mesenteric glands; ulceration of epiglottis; lung emphysema and congestion (hypostatic). Polyinfection with bacteria.*

Body 164 cm. long, strongly built and well nourished. At different points on the body congested areas are apparent and a few darker and smaller injected points. The abdomen is distended, the blood vessels of the neck turgid and contain with fluid blood. Muscles well developed and deep red in color.

Peritoneal cavity.—On incision there is a free escape of gas. The upper portion of the small intestine is greatly distended. The blood vessels of the serosa over the whole peritoneum are injected; the serosa itself is cloudy, and coagula of fibrin, loosely adherent, are scattered over it. In the dependent parts of the cavity about 200 cc. of turbid, yellow fluid are contained. *A perforation 2 mm. in diameter is found, located in a loop of intestine, situated in the left iliac fossa.*

Intestines.—The large intestine is firmly contracted; its mucous membrane is pale, and it contains tolerably firm, yellow fæcal masses. The vermiform appendix is somewhat dilated, and in the swollen mucous membrane several superficial small ulcerations are apparent. The largest number of losses of substance is found in the ileum; the most advanced ones are situated at the ileo-cæcal valve. The mucosa of the valve itself is ulcerated. The ulcers are surrounded by swollen edges which are undermined, and in their clean bases the circular muscular tunic is visible. A small quantity of necrotic material is found still adherent to a very few of the ulcers. Between the ulcers are swollen solitary and agminated follicles. Situated 22 cm. from the valve there is an ulcer 2 cm. in diameter, the clean base of which is formed by the circular muscular coat, whose edges are necrotic and in the centre of which there is a perforation 2 mm. in diameter. The first losses of substance are found in the upper part of the jejunum.

The stomach contains dark-brown contents. Its mucous membrane is apparently normal.

Mesenteric glands.—Enlarged, congested and softened.

Spleen.—Bound to diaphragm by old adhesions, which cannot be broken down without lacerating the organ. It weighs 510 grams; the capsule is covered in part with fibrinous coagula; the consistence is moderately firm. On section it presents a dark brown color, and the Malpighian bodies are prominent.

Liver.—Capsule covered with fibrinous masses; otherwise it is smooth. On section it is pale, the lobules fairly distinct; no increase in fibrous tissue. Weight 1870 grams.

Kidneys.—Both of approximately the same size and general appearance. Together they weigh 510 grams. The surface is smooth; the capsules stripping off readily, and the stellate veins are injected. On section the striæ are visible; the glomeruli are easily seen; the cortex generally is pale and varies in thickness from 5 to 7 mm.

Adrenal glands and pancreas apparently normal.

Heart.—No valvular lesion; coronary arteries smooth; myocardium pale and soft. Weight 240 grams.

Lungs.—Free from adhesions; a small amount of fluid in each pleural cavity; the posterior borders of the lower lobes are intensely congested. The upper lobes are moderately emphysematous. The bronchi are intensely congested.

This case derives especial interest from the bacteriological examination. It illustrates to what extent a mixed infection with bacteria may occur in human beings. Of course the infection atrium was the intestine, the perforation found there opening the way for the escape into the peritoneal cavity of a considerable variety of microorganisms which happened to be present in its lumen. Soon the several kinds, although perhaps not equally, made their way into other parts and organs, and this very difference between those bacteria present in the peritoneum and those found elsewhere in the body is not without its instructive side. I cannot help holding up as an example the present case in comparison with the first two of our series in support of the fact that the conditions which enable the typhoid bacillus to flourish, if not to exist at all in the blood, must be very peculiar. As will be seen shortly in this case the typhoid bacillus found its way with other bacteria into the peritoneal cavity, and there seems to be no reason why it should not have been spread with the same facility through the body as its associates; and yet its distribution at autopsy was by no means so universal as some of the other forms.

The close association of the typhoid bacillus and the colon bacillus in this case will be remarked. With respect to the means used to separate them I would again refer to the remarks on this subject in the first case. In the course of the study of this case it was necessary to make many plate, roll and other cultures, and to keep the organisms under observation for considerable periods of time; and yet after certain colonies, existing side by side perhaps, in the original plates, had been isolated, and through their properties determined to be colon or typhoid, no transition of one to the other could be detected in the subsequent study of these forms.

The method pursued in the isolation of the several bacterial species was the use of various media and plate and roll cultures. Many hundred colonies were examined microscopically and grown upon all sorts of culture media with the result of separating the following forms from the different situations mentioned.

a. Bacilli, varying in length, short forms 2 to 3 times as long as broad; larger forms several times as long as broad. Colony growth upon agar-agar and gelatine resembles colonies of typhoid bacilli. They do not coagulate milk after several weeks; on potato the growth is either invisible or slight, moist, showing little tendency to spread, and of yellowish-brown color. Drop cultures 24 hours old show active motility. No indol production. Does not ferment sugar. Bacillus typhoideus.

b. Bacilli, a little coarser than the preceding, all or nearly all are of the short form. Colony growth on agar more opaque than last; on gelatine it forms thin filmy surface colonies which show a blue translucence. Visible luxuriant growth upon potato of brownish-yellow color. Drop cultures 24 hours show no perceptible motility. Produces indol; ferments sugar. Bacillus coli communis.

c. Cocci, growing readily on all the culture-media, in the form of grape-like clusters. On potato an abundant yellow growth; in gelatine stick culture rapid liquefaction. Staphylococcus pyogenes aureus.

d. Minute white colonies showing no tendency to spread, but a little larger when on the surface than in the depth of the culture media; cover-slips show them to be composed of chains of cocci. Streptococcus pyogenes.

e. Bacilli, variable in length, motile, rapidly coagulate milk, quickly liquefy gelatine; colonies spreading (migrating). Proteus vulgaris.

These organisms were distributed in the following manner:

Peritoneal cavity.—Bacilli typhi abdominale, coli communis, proteus vulgaris. Staphylococcus aureus; streptococcus.

Mesenteric glands.—Pure culture of the typhoid bacillus.

Iliac lymph glands.—Typhoid and colon bacilli.

Retro-peritoneal lymph glands.—Typhoid and colon bacilli.

Spleen.—Pure culture of the typhoid bacillus.

Liver.—Typhoid bacillus and streptococcus.

Bile.—Pure culture of the typhoid bacillus.

Kidneys.—Bacillus coli communis and streptococcus.

Lungs.—Pure culture of the bacillus coli communis.

Blood.—Taken from the azygos vein. Bacillus coli communis and streptococcus.

Thoracic duct.—Bacillus coli communis and streptococcus.

Ulcer of intestine.—Bacillus typhoideus; bacillus coli communis; bacillus proteus vulgaris, and streptococcus. The colon colonies predominated.

CASE V.—*Typhoid fever with perforation (3rd week of disease); acute peritonitis; general streptococcus infection. Absence of typhoid bacilli from the cultures.*

This case is included as illustrating the importance of the secondary micro-organisms in typhoid fever, even after the disappearance from the body of the typhoid bacilli. Although the disease was yet at its height, the evidence of the cultures in this case is to the effect that the typhoid organisms themselves had either entirely disappeared or were so few in number that they were not transplanted with the tissue juices to the culture media.

Henry R., æt. 35, white, admitted to the medical wards (Dr. Osler) November 1st, 1892, complaining of chilly sensations and fever.

The patient's father is living and well; the mother died of pneumonia (?). One brother and one sister living; none dead.

He had measles when a child, but since that time he claims to have been healthy up to the present illness.

The present illness began about one week ago with pain in the back of the neck, stiffness of knees and a sense of fatigue. Four days ago he felt giddy and generally badly. No cough or expectoration. For the past five days he had been in bed constantly. Examination of the blood showed no malarial organisms.

November 2nd.—Temperature 104°, pulse 120, respiration 32. Yesterday afternoon the skin was flushed, hot and dry, and over the trunk a well-marked, but faint roseola could be seen. Spleen palpable; tongue dry and coated. This morning the pulse is 112, and slightly dicrotic. Thorax clear throughout. Heart.—Point of maximal impulse not to be distinctly localized; cardiac flatness entirely obliterated by pulmonary resonance. Sounds are heard loudest in about normal position in 5th space, and appear of normal relative intensity. Liver border not palpable; abdomen not distended. There is slight tenderness in the ileo-cæcal region; some gurgling; no distinct rose-spots; urine brownish-yellow, clear, acid, specific gravity 1026, distinct trace of albumen, diazo-reaction present, epithelial cells, leucocytes and granular casts seen; no sugar. Blood.—Leucocytes 8,500.

November 8th.—The temperature between the 4th and 8th ranged between 100.6° F. and 104.2° F. Last night, during the bath, the patient had an involuntary movement and the pulse became very weak. Since midnight the temperature has not been below 103.6° F. This morning the patient is rational, but the pulse is rapid; at the time of the visit, it was 144. Tension and volume not bad. The abdomen is not especially distended, but it is held very tense, and is generally tender. A number of typical rose-spots are present. Later note. For the past 18 hours the temperature has reached 104° F. The patient is less bright than he was, but there is no delirium. Pulse 130, tension low. The abdomen is much distended, especially in the epigastric region, which is very prominent. The patient sank during the evening and died at midnight. Note by Dr. Osler: "When I saw the man at 12 o'clock, noon, there were no marked symptoms of collapse. The pulse was rapid, but not small; face not pinched or anxious, and he answered questions readily. There was no pain in the lower abdomen. The tympany was higher than I have ever seen."

Autopsy 10 hours post mortem.

ANATOMICAL DIAGNOSIS.—*Typhoid fever (early and late ulcers) and swelling of follicles; perforation; fibrino-purulent peritonitis; acute splenic tumor; parenchymatous degeneration of viscera. General infection with streptococci.*

Body 160 cm. long; well-nourished; subcutaneous fat in moderate amount; muscles deep brownish-red in color.

Peritoneal cavity.—On incising this cavity there is an escape of foul smelling gas. The surface of the intestines are much injected. In the cavity there are about 1000 cc. of turbid fluid. Covering the loops of the intestine occupying the right iliac region are flakes of fibrin. A small perforation occurs in one of the loops of intestine in this situation from which a yellowish semi-solid fæcal mass protrudes into the peritoneal cavity. The diaphragm on the right side is at the 3d intercostal space; on the left side at the 4th rib.

Intestines.—Beginning with the ileum, the patches of Peyer are swollen. At a distance of 80 cm. above the valve an ulcer measuring 5 x 2 mm. is situated which passes through all the coats of the intestine in its midportion, the perforation being 1-5 mm. in diameter. The edges of this ulcer are undermined and its base quite clean. From this point downwards the solitary follicles are all swollen, and in the centres of some of these small losses of substance have occurred. The ulcers are very few in number until the valve is reached; here they are quite numerous, larger and extend to the circular muscular coat. Some of these have undermined edges, and while in some the slough has been completely removed, to others dirty necrotic material still adheres. Neither the vermiform appendix nor the large intestine contains any ulcers.

Mesenteric and retro-peritoneal glands swollen and congested.

Spleen.—Enlarged; it weighs 750 grams; its capsule is wrinkled, and on section it is soft, of a brownish-red color, the pulp is abundant, and the Malpighian bodies are easily visible.

Liver.—Weighs 2400 grams. The surface is smooth, except over the right lobe, where there are several depressed spots which on section present a dark hæmorrhagic appearance. On section it is opaque, of a yellowish color; the lobules are invisible.

Kidneys.—Together they weigh 450 grams. Surface smooth and pale; stellate veins prominent. On section striæ obscure, cortex pale, its average thickness being 8 mm.; the glomeruli are visible and red in color.

Heart.—Weight 300 grams. All the valves normal; myocardium of a brownish-red color and firm consistence.

Lungs.—Free from adhesions, except a few light ones over the right lobe. On section they are moderately congested and œdematous. Mucous membrane of bronchi congested.

The pancreas, adrenal glands, stomach, testicles and bladder apparently are normal.

Frozen sections.—Kidneys.—No increase of the connective tissue. The epithelium of the convoluted tubules is swollen and granular, and a few of these tubules are quite fatty. A very small amount of fine fat can be made out in the glomeruli.

Liver.—The liver cells are swollen and granular; the Kuppfer's cells are fatty. No connective tissue increase. Many so-called "lymphomata" are present. These latter very in size and appearance. The larger show, in addition to the necrotic cells, much detritus; the smaller show only hyaline liver cells. Surrounding these foci the liver cells are very fatty.

Bacteriological examination.—Cover-slips from the peritoneum show many streptococcus chains which were usually short, and bacilli of apparently only one species. Cover-slips from the spleen negative.

Cultures.—Agar-agar Esmarck rolls were made from the fluids and viscera.

Peritoneum.—Colonies of the streptococcus and the bacillus coli communis.

Retro-peritoneal lymph glands.—Streptococcus colonies.

Spleen.—Two streptococcus colonies only.

Bile.—One colony of the streptococcus.

Kidneys.—Streptococcus and bacillus coli communis. Former predominate.

Lungs.—Many colonies each of streptococcus and bacillus coli communis.

Heart's blood.—The roll is thickly studded with streptococcus colonies. No other kind of micro-organism present.

There can, we think, be little doubt but that the perforation of the intestine, the peritonitis and subsequent death were in this case directly attributable to secondary infectious agents, especially with the streptococcus pyogenes.

CASE VI.—*Typhoid fever; death from hæmorrhage (sixth week of the disease). Disappearance of the typhoid bacilli. Infection with bacillus coli commune.*

Wallace H., colored, aged 23, admitted to the medical wards (Dr. Osler) July 1st, 1895, complaining of pain in the head, stomach and shoulders.

The patient states that his father died of dropsy. His mother is living and well; the same is true of four brothers and four sisters, with the exception of one brother, who has rheumatism. Two brothers died in infancy.

He states that as a child he had measles, mumps, whooping-cough, chicken-pox, but has not been ill since that time.

His present illness dates two weeks prior to his entrance, and was ushered in with a violent headache over the frontal and occipital regions. Soon afterwards he complained of pain in his stomach, which has continued up to the present time. He has vomited several times. About one week ago he had profuse epistaxis. For ten or twelve days he has had diarrhœa.

July 1st.—The patient is found to be a large, well-made, well-nourished man. Dorsal decubitus is present. The skin is dry and smooth; eyes dull; color of mucous membranes good. The tongue is coated. There is marked abdominal tenderness on pressure, particularly in the lower parts. The spleen is palpable. The thorax is clear. The heart's impulse is seen at the fifth space in the nipple line. On auscultation the first sound is replaced by a rumbling, soft systolic murmur, which is transmitted to the axilla. The second sound is clear and loud. The second pulmonic is accentuated; the second aortic fairly loud and clear.

July 2nd.—Pulse is 22 to the quarter, markedly dicrotic. On the back of the arms there are a number of slightly raised papules. Respiration is clear; the splenic flatness is practically obliterated by abdominal tympany.

July 4th.—The splenic flatness is increased, beginning at the eighth rib and extending to the eleventh costal margin. The border is not palpable. Patient appears drowsy.

July 11th.—Temperature is still elevated, but falls after baths. General condition appears somewhat better.

July 17th.—The stool to-day was semi-fluid, of a bright yellow color, containing a small quantity of bloody mucus and a few milk curds.

July 22nd.—Since the last note the condition of the patient has remained about the same. The temperature on the 18th and 19th ranged a little lower, the registered pulse having been for three days below 100. At about 7.40 a. m. on the 23rd the patient had a stool of bright, fresh blood, appearing to be about a quart in quantity. Fifteen minutes later he had another stool of about one pint of clots; fifteen minutes after this a third stool of a pinkish fluid character. The temperature at 8 a. m. was 98.2°. Almost immediately after the hæmorrhage the patient became almost pulseless, and rapidly sank in spite of all stimulation, dying about 8.30.

Autopsy five and a half hours post-mortem.

ANATOMICAL DIAGNOSIS.—*Typhoid fever (ileo-typhus and colo-typhus); death from hæmorrhage; acute splenic tumor; parenchymatous degeneration of the organs.*

Body of a well nourished man, 169 cm. long; rigor mortis in the extremities; the surface and mucous membranes very pale; muscle dark red in color.

Peritoneal cavity contains a small amount of clear fluid. The mesenteric and retro-peritoneal glands are swollen and slightly congested.

Intestines.—Beginning 280 cm. above the valve there is a series of ulcers, the first being discrete and superficial, the lower ones larger, confluent, deeper, in many instances exposing the muscular coat of the intestine. Just above the valve there is a large mass of ulcerations involving nearly the whole of the intestine at this part. For the most part the ulcers are clean; a few of the superficial ones still contain the remains of the necrotic mucous membrane. The colon and rectum show superficial ulcerations similar to those found in the small intestine. These are quite numerous. The large intestine contains in its lumen a considerable amount of fluid blood. The eroded blood vessel was not found.

The spleen weighs 350 grams; the capsule is smooth; consistence is soft; on section it is dark red in color, and almost diffluent. The Malpighian bodies are very indistinct.

The liver weighs 2130 grams; the surface is smooth; on section the organ is homogeneous, of a yellowish color; the lobules being very indistinct.

The kidneys are the same in size and general appearance, and together they weight 320 grams. The surface is pale; on section the cortex is pale, swollen, averaging 9 mm. in thickness; the striæ are indistinct, and the glomeruli are pale. The other organs present no especially remarkable condition.

Cultures were made from the heart's blood, and the various organs upon agar-agar. The plates from the liver, kidneys, bile and blood remained sterile. Those from the lungs and spleen contained numerous greyish-white colonies which were composed of short, plump bacilli, giving all of the reactions distinctive of the bacillus coli communis. Numerous attempts to isolate the typhoid bacillus, involving the examination and study of a large number of colonies from these plates, were entirely unsuccessful.

It is not an uncommon observation in cases of typhoid fever which have terminated fatally, late in the course of the disease, at a time when the ulcers in the intestine have become entirely, or for the most part clear, and healing has already begun, to find that the typhoid bacillus refuses to be cultivated from the tissues including the peritoneal lymphatic glands. The bacteriology of these cases may lead to some confusion concerning the fixity of the typhoid species of organism if it should so happen that in place of the typhoid bacillus forms with the properties of the bacillus coli communis are met with, unless it be borne in mind that the colon group of organisms finds the lesions existing in the intestinal wall very favorable for their emigration. At least the cultivation from these cases of colon bacilli should never awaken the suspicion that the two species are transmutable. For we now know, thanks to the observations upon the bacillus coli communis by Dr. Welch, that lesions of far less severity than are present in these cases suffice for their escape from the intestinal canal and their dissemination throughout the body. The present case is cited as an example in which, after the entire disappearance of the typhoid bacilli from the body, so far as failure to demonstrate them in cultures can be taken to exclude their presence, the colon bacilli were found in the tissues at autopsy.

VI.—AN INVESTIGATION INTO THE SO-CALLED LYMPHOID NODULES OF THE LIVER IN TYPHOID FEVER.

BY WALTER REED, M. D.,
Surgeon U. S. Army.

(*From the Pathological Laboratory of the Johns Hopkins University and Hospital.*)

The pathological changes met with in the liver of those who have died of typhoid fever have, for a long time, attracted the attention of investigators. Perhaps to Friedreich * should be given the credit for the discovery of certain circumscribed nodular formations which he described as occurring in the liver of a girl, twenty-one years of age, who had died of typhoid fever. He found in the neighborhood of the coarser bands of stroma, collections of cells which could not be seen with the naked eye, but which, viewed microscopically, consisted of round and partly irregular cells imbedded in the connective tissue of the organ. While this description is not complete, since Friedreich only saw these collections of cells in the interstitial connective tissue, yet it is, we think, sufficiently accurate to justify the belief that he saw what E. Wagner,† three years later, so minutely described. The latter's classical description of the hepatic lesions seen by him in five patients who had died of typhoid fever has scarcely been added to up to the present time. As regards his first case, Wagner describes the liver as of normal size and anæmic in appearance, somewhat softened, and with the outlines of the lobules obscure. He saw over all portions of the organ quite numerous, small areas, which were just on the limit of visibility, of a gray color, and fairly solid in character. This refers to the naked-eye appearance. Upon microscopical examination these spots were found to be round, oblong, sometimes irregular, serrated and biscuit-shaped, the majority of them occupying the actual parenchyma of the organ, and replacing the hepatic cells. Now and then they invaded the interlobular connective tissue. They consisted of closely lying groups of small, round and oval refractive nuclei; in some places, on the periphery of the area masses of these nulcei, of pointed shape, projected into the surrounding liver tissue. Wagner was of the opinion that these nuclei were derived partly from the cells of the interacinous connective tissue, and that in part they had their origin within the lobules. He was unable to completely demonstrate the manner of production last mentioned, but thought that these nuclei owed their origin to the nuclei of the liver cells. In a second case of typhoid fever, Wagner* saw these fine, barely visible, sharply circumscribed grayish specks over all parts of the cut surface of the liver. As a rule they were immediately on the periphery of the small portal veins, and consisted of albuminoid molecules between which small round refractive nuclei were quite regularly distributed, and in contrast with the central part of the area, which appeared to consist of irregular particles, the periphery was largely made up of round nuclei.

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* Ein neuer Fall von Leukamie, Virchow's Archiv., 1857, Band XII, S. 53.

† Beiträge zur pathologischen Anatomie der Leber bei Abdominal Typhus, Archiv d. Heilkunde, 1860, Band I, S. 322.

The third case investigated by Wagner† is of interest in connection with our own investigations. The patient had recovered from an attack of typhoid fever, but had died from some other disease two and a half months later. The characteristic nodules were not found in this case, and the inference is drawn that they had been present, but had entirely disappeared, their place being probably taken by a new formation of liver cells.

Hoffmann,‡ referring to the previous investigations of Wagner, states that he has also found in a considerable number of cases of typhoid fever small grayish nodules in the liver, and says that in most cases it requires close inspection in order to see them with the naked eye; that in some cases they are quite distinct, and on the cut surface, appear as flat elevations; microscopically they appear as round conglomerations of small round cells and nuclei, resembling the lymphoid nodules found in the peritoneum. He states that their location is, in most cases, within the lobules, and close to one of the small portal spaces. He found, almost without exception, a diffuse infiltration of cells which followed the ramifications of the portal vein. He regards them as lymphoid cells which have wandered in from the portal vein. He observed these nodules in the liver in 38 of 250 cases examined, and in 14 of the 38 the nodules could be seen with the naked eye.

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* Die Körnchenbildung in der Leber, Arch. d. Heilkunde, 1861, Band II, S. 103–114.

† Beiträge zur Pathologie und pathologischen Anatomie der Leber, Deutsches Archiv für klin. Med., 1883–4, Band XXXIV, S. 520–537.

‡ Untersuchungen über die pathologisch-anatomischen Veränderungen der Organe beim abdominal Typhus, Leipzig, 1869, S. 221–222.

Orth * states that the microscopic gray nodules found in the liver of typhoid fever are of the same formation as those seen in leukæmia and lymphadenomata.

Fraenkel and Simmonds, † while studying the hepatic changes in abdominal typhus, always found lesions which they considered to be intimately connected with the disease, viz., small cell infiltration of the connective tissue, and those peculiar formations generally known as lymphomata. They describe two forms which they think are deserving of the latter term: First, those areas which consist of closely packed small, round cells, amongst which may be recognized, here and there, liver cells. Secondly, those in which the round cell accumulation is less close, and which appear to consist largely of the remains of poorly staining liver cells. There are also small, circumscribed areas of liver tissues, in which the protoplasm and nuclei of the cells only stain imperfectly, or not at all, and which do not deserve to be designated as lymphomata. They are inclined to consider this latter form as one of coagulation necrosis. They are further of the opinion that in the beginning the change is one of circumscribed degeneration, and that later there takes place an accumulation of round cells within the necrotic area. They regard as improbable any direct connection between the presence of typhoid bacilli and these formations, although they once found a clump of the bacilli within an affected spot.

Handford ‡ states that in all fatal cases of typhoid fever examined by him there were found definite changes in the liver, in the form of parenchymatous and interstitial changes. The most characteristic

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* Lehrbuch der speciellen pathologischen Anatomie, 1887, Band I, S. 954.

† Die ætiologische Bedeutung des Typhus Bacillus, Leipzig, 1886.

‡ "Hepatitis in Enteric Fever." Transactions of the Pathological Society of London, 1889, pp. 129–132.

change, though not constant, is the presence of small, round areas that stain imperfectly, that are infiltrated more or less thickly with leucocytes, and that are surrounded by a dense ring of cellular infiltration. The liver cells in the patches show cloudy swelling or more advanced degeneration. In more advanced stages the liver cells cannot be distinguished at all, and mingled with the leucocytes are irregularly shaped and spindle cells. In fact the tissue resembles an early stage of cicatricial tissue. In a third variety the patches cannot be distinguished from miliary abscesses. Handford regards the last as a septic hepatitis, due to absorption of septic particles from the intestine, while the former are due to capillary embolism. He is not satisfied that any specific bacillus is the cause of these lesions.

Siredey * states that during the course of the second week, and sometimes during the third week of typhoid fever, the microscopical appearance found on section of the liver is so peculiar and distinct that one can, in the majority of cases from these appearances alone, make a diagnosis of that disease. He describes them as being scattered in various parts of the hepatic substance, and says that their form, location, and size are extremely variable; that while ordinarily round, they are sometimes ovoid or even star-shaped. They are oftener met with at the centre and in the midst of the lobule than at the periphery. He remarks that they offer the greatest analogy in their general shape to tuberculous nodules; but they do not present the distinct layers found in the latter, nor does one see giant cells, nor epithelioid cells. He states that he has never seen any tendency to caseation in these nodules; that they never include hepatic cells, and that the cells composing them are but little, if at all altered. He further says that although these nodules are perhaps special to typhoid fever, and that when once encountered in the liver the diagnosis is probable, yet there are other infectious maladies characterized by the migration of lymphoid cells into the liver, and that these can under certain circumstances present themselves as nodular conglomerations. He expresses the probable opinion that after convalescence the liver parenchyma is fully restored to its former integrity without any lesion being left behind.

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*Contribution a l'études des alterations du foie dans les maladies infectieuses, Rev. de Méd., VI, Paris, 1886.

Legry* has contributed an interesting monograph to this subject. In addition to a study of the lesions found in the human liver in typhoid fever, he has injected pure cultures of typhoid bacilli into the mesenteric vein of rabbits, and afterward investigated the change, if any, found in the liver. The fact is worth mentioning in this connection, that our experiments on rabbits, carried out in much the same manner as Legry had done, were completed prior to our acquaintance with his monograph, and that while his experiments were attended with negative results as far as finding any changes in the rabbit's liver are concerned, our own experiments were followed by characteristic lesions, as will be later shown. He gives much the same general description as to the location of these nodules as Siredey had already done; but does not agree with him that they consist of lymphoid cells. He supports the conclusion that these nodules, which are found most often along the portal spaces, are always formed of nuclei, generally abundant, surrounded by a granular substance, which latter appears to result from the degenerated protoplasm of liver cells. He gives no definite opinion as to the source of these nuclei, but thinks that the nodules have a bacterial origin. He never found the bacilli within the nodules, but has found upon section, six times in eleven cases, characteristic clumps of typhoid bacilli. His experiments upon rabbits (two cases) gave no definite results.

It will thus be seen that each of the writers to whose investigations we have referred describe, with more or less particularity, certain nodular formations found in the liver of those who have died of typhoid fever.

Our own investigations have been carried on in the Pathological Laboratory of the Johns Hopkins University, and have consisted in a careful study, microscopically, of the livers of five patients who had died of typhoid fever in the wards of the Johns Hopkins Hospital. We have also injected pure cultures of typhoid bacilli into the mesenteric vein of rabbits, and afterward studied the lesions found in their livers.

Before we proceed to a description of the microscopic appearances we wish to state that although it is not always possible to distinguish with the naked eye the nodular formations which Wagner discovered macroscopically, yet a patient search of the cut surface of the organ will generally be rewarded by finding here and there very small, roundish, grayish-white specks within the lobules; sometimes they are quite abundant and easily to be seen—again just on the limits of visibility, and with difficulty found.

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* Contribution a l'étude du foie dans le fievre typhoide, Paris, 1890.

MICROSCOPIC APPEARANCE OF THE LIVER.—In two of the cases studied by us frozen sections of the fresh liver were made. In addition to the well-marked fatty infiltration of the cells, the latter being generally filled with large fat drops, there were also to be seen within the lobules well-defined areas which contained many fatty granular cells situated in the midst of a coarse granular material. Within these areas there were also to be observed many irregular-shaped nuclei.

For the further study of the microscopic appearances the following method was used, viz.: Fresh portions of the liver were hardened in 95 per cent. alcohol, and afterward imbedded in paraffin or celloidin. Sections of these were then stained with Löffler's methylene-blue solution for ten to thirty minutes; then transferred to ½ per cent. aqueous solution of eosin, where they remained from fifteen to forty-five seconds; next decolorized and dehydrated in absolute alcohol, cleared in oil of cloves or bergamot, and mounted in Canada balsam.

If, as is sometimes the case, we are unable to see with the naked eye the small whitish areas on the cut surface of the liver of typhoid fever, when we come to the microscopical examination of the organ we no longer experience any difficulty in finding them. If one has succeeded in obtaining a properly stained section a most striking picture is presented to the eye when examined with the low power, and that feature of the picture which will most quickly fix the attention is the presence of bright, sharply defined eosin-stained areas of various shapes and sizes, which are to be seen scattered plentifully throughout the section, and in almost every field. Sometimes these areas are almost perfectly round, more often oval, and generally irregular in outline. The sizes of these foci are as variable as their shapes, embracing now only a few liver cells, again involving as much as one-half or even the whole of a lobule. Their relative position is also very variable; sometimes we find them near the portal spaces—again in the midst of the lobule, and quite as often situated near the central vein. We have several times observed an area occupying the entire periphery of the central vein. It cannot be said, we think, that these areas stand in closer relation to the portal vein than to the hepatic spaces. If the section has been well stained there should never be any difficulty in picking out even the smallest necroses, since the contrast between the healthy cells, which are stained with methylene-blue, and the necrotic eosin-stained cells is always well marked.

The appearance of these areas is variable. Sometimes we see a spot involving as much as one-fourth of a lobule in which the liver-cells have apparently died *en masse*, but continue to retain their shape perfectly; even the demarcation between the individual cells can still be plainly made out. The beam-work of the cells will not be at all broken, but will be seen to be continuous with that of the surrounding healthy cells. The capillaries of such an area will be found to be unaltered, or perhaps slightly dilated. Continuing the examination with the low power, we will most often fail to discover any nuclei whatever within the finely granular eosin-staining cells; and even with a high amplification may only find within these cells minute particles of nuclear detritus. We have seen several such areas as the one now being described, in which there appeared no increase whatever of the cells within the capillaries situated between the rows of necrotic cells. In other instances we have found the capillaries to contain a considerable number of polynuclear leucocytes. Sometimes we have seen a marked increase of polynuclear cells within the capillaries, near the centre of the area; again, the largest number will be found about the periphery of the necrosis. We are inclined to regard the areas just described as probably the earliest form of the local parenchymatous degeneration. These are the areas which Fränkel and Simmonds consider to have undergone coagulation necrosis, and which, in their opinion, do not deserve to be designated as lymphomata.

Far more frequently one will see areas wherein the liver cells no longer preserve the regularity of their framework, but have become displaced and have lost their shape. Some of these cells may still show pale and swollen nuclei, but the majority will have entirely lost their nuclei, and in their stead there will be discovered within many of the necrotic cells one or several polynuclear leucocytes. *The presence of the irregular and club-shaped nuclei within the necrotic cells of the area is one of the most striking and important features to be observed.* Although certain areas may show only a small number of such nuclei, as a rule they are found in great abundance. We have never, however, observed such an abundance of polynuclear leucocytes within a necrosis in the human liver as to give the picture of a miliary abscess such as is described by Handford. Sometimes we find included within such an area, and completely surrounded by the necrotic cells, from one to a dozen or more apparently healthy liver cells which still preserve their nuclei, and which do not stain with eosin. These cells, as a rule, contain many fat drops, but in this respect do not differ much from the cells throughout the section.

In addition to the two varieties of areas described we will find others which have undergone yet further changes. Here the hepatic cells have quite disappeared, and are replaced by numerous small, round, deeply-staining nuclei, which crowd the area in all parts, intermixed with fewer oval, spindle-shaped nuclei. In other words, the appearance is that of young connective tissue, as mentioned by Handford.

Besides these larger areas of necrosis, we wish to invite attention to the smaller necroses which are found in the liver. We here refer to the necrosis of individual liver cells. We have found these smaller necroses in each of the cases examined by us. In one case they were a prominent feature of the examination. We find scattered here and there amongst the healthy cells of the lobule one or more cells whose protoplasm stains brightly with eosin, and whose nuclei have, as a rule, entirely disappeared. We will generally observe that such necrotic cells contain within them several irregular-shaped nuclei, which plainly mark the entrance of polynuclear leucocytes into them.

RELATION OF BACILLI TO AREAS OF NECROSIS.—We have found characteristic clumps of typhoid bacilli upon section in each of the five cases examined by us; it was generally possible, by careful search, to find one or more colonies in nearly every section, the bacilli lying always within the capillaries. As to the relation existing between these clumps of bacilli and the necrotic areas, we have examined a great many sections from each case, but have only succeeded in finding the bacilli within the areas five times. Four times the colony lay just within the margin of the area; in the remaining instance we observed a capillary distended to twice its normal size by a large colony of bacilli, which was surrounded on all sides by necrotic liver cells, so that the clump of bacilli occupied in this case the centre of the necrosis. We were at first inclined to believe that the finding of the colony of typhoid bacilli within the necrotic area was sufficient reason for assuming that the death of the liver cells was due to the presence of the bacilli, or rather that the toxalbumin produced by the latter caused the death of the cells in their immediate vicinity. When, however, we had examined very many areas in which no bacilli could be discovered, and when we found colony after colony surrounded by liver cells, which, to all appearances, were quite healthy, we were reluctantly compelled to leave in abeyance so plausible a theory. With the object, if possible, of coming to a final decision in this matter, we made careful serial sections in two of our cases, but prolonged and careful search failed to discover any bacilli within these areas.

Considerable interest must attach to the final disposition of these localized necroses of the liver in those who have recovered from typhoid fever. One is struck with the large number of necrotic cells which must necessarily be removed and whose places must be filled by other cells. Siredey makes the rather surprising statement that during the third week of the disease these nodules no longer appear in the liver; as he believes that they consist largely of lymphoid cells which have been brought to the liver through the portal circulation, he supposes that by the third week they have already re-entered the general circulation. This supposed disappearance of the nodules during the period above mentioned is not borne out by observation, as we have found these lesions in the human liver as early as the second week of the disease, and as late as the seventh week after the attack had begun. Wagner states that they probably entirely disappear, and suggests a restoration of the tissue through a proliferation of the liver cells. While our investigations were being carried on we were so fortunate as to be able to examine microscopically the liver of a patient who had experienced an attack of typhoid fever about twenty-five years prior to death. This was the case of a woman aged about seventy years, who died of carcinoma of the ovary and was autopsied in the pathological laboratory of the Johns Hopkins Hospital. The clinical history of a former attack of typhoid fever was fully supported by finding in the lower ileum several large cicatrized areas, with raised, uneven edges. Microscopical examination of the sections taken from these old cicatrices showed that an ulcerative process had destroyed the mucosa in its entire thickness, and had extended down to the muscular layer. No muscularis mucosæ was to be seen; each ulcer had occupied the greater part of a Peyer's patch, and it was extremely interesting to observe that the follicles of Lieberkühn had been somewhat reproduced, these appearing as much atrophied follicles resting directly on the muscular layer. Equal interest attached to the microscopical examinations of the hardened sections of the liver, for, aside from the general atrophy of the liver cells (the patient was quite old), there were to be seen in almost every field from one to three circular, round, ovoid, or irregular-shaped areas of dense connective tissue. These were, as a rule, sharply defined, being situated sometimes near the portal spaces, again around the hepatic vein, and often *within the lobules;* so that as regards relative position they corresponded to the areas of necroses found in the liver of typhoid fever. Within many of these old areas of connective tissue, blood vessels and bile ducts had been reproduced. While it would not be well to attach too much importance to the localized areas of connective tissue found in the liver in this case, we yet consider it of extreme interest to find such an unusual form of cirrhosis in the liver of a patient who had so clearly passed through a former attack of typhoid fever.

LESIONS IN THE LIVERS OF RABBITS INOCULATED WITH PURE CULTURES OF TYPHOID BACILLI.—Blackstein * failed to discover any lesions in the liver of rabbits into whose circulation he had injected pure cultures of typhoid bacilli. Legry and Pavone † only found fatty degeneration of the liver cells and of the endothelial cells of the capillaries.

In order to throw further light upon the necrosis found in the human liver, we have injected pure cultures of typhoid bacilli into the mesenteric vein of rabbits, this procedure sufficing to carry the bacilli at once into the hepatic circulation, giving them an opportunity to exert their full effect upon the parenchyma of the liver. The cultures were in plain or one per cent. glucose bouillon, and were from twenty-six hours to twenty days old. The culture which was used for these experiments had been obtained from the spleen of a patient who had died of typhoid fever in the Johns Hopkins Hospital, and had been thoroughly tested as regards its growth on the customary media.

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* "Intravenous Inoculation of Rabbits with the bacillus coli communis and the bacillus typhi abdominalis," Johns Hopkins Hospital Bulletin, July, 1891, No. 14.

† "Nuovi Punti di vista nello studio della quistione del potere patogeno del bacillo del Tifo degli anamali da sperimento." Giornale Internacionale delle Scienze Mediche, 1888.

The method of procedure was as follows: The animal having been first etherized, a laparotomy was done under strict antiseptic precautions, and an injection of the culture was then made into one of the larger mesenteric veins by means of a sterilized Koch's syringe; the wound was next carefully closed with silk stitches, and celloidin dressing placed over the line of incision. Although we laparotomized thirteen rabbits, in only ten of these was the injection of the culture into the circulation satisfactorily done. In one of the three unsatisfactory cases the hæmorrhage following the withdrawal of the needle was of such amount as to call for the use of a ligature, which was followed by hæmorrhagic infarction of the bowel and premature death of the animal. In one case the culture was accidentally injected between the layers of the mesentery, and in one case an attempt was made to inject the culture into one of the smaller branches of the mesenteric artery, which was also followed by hæmorrhagic infarction and early death of the animal. We will now give brief protocols of some of our experiments.

Experiment No. 1, May 12, 1891, 10 a. m.—Small white rabbit; 0.3 c.cm. of a twenty-six hours' old culture of typhoid bacilli in plain bouillon injected into one of the larger mesenteric veins; May 14th, 10 a. m., forty-eight hours after injection, the rabbit was killed. No peritonitis; stomach contained a large quantity of food; moderate amount of fluid fæces in small intestine; no enlargement of Peyer's patches or solitary follicles; spleen small, dark red; kidneys normal; liver shows beneath the capsule, on upper and lower surfaces a few roundish or irregular-shaped whitish nodules, 1 to 2 mm. in diameter; there are also to be seen many very minute yellowish dots beneath the capsule and on the cut surface of the organ. Frozen sections show the larger areas to contain coccidia; small areas, however, do not contain these parasites, but are crowded with many fatty granular cells. Cover-slips from blood, liver, spleen, and kidneys negative; cultures (gelatin plates) from blood, liver and spleen show numerous colonies of typhoid bacilli; kidney plate negative. Hardened sections of liver stained with methylene-blue and eosin show, in addition to the areas containing coccidia, many small foci of cell necrosis. These are situated within the lobules. The liver cells within the area have lost their nuclei; but the beam-work of the cells is as yet unbroken; while in some areas a few polynuclear leucocytes are seen within the capillaries, in others the capillaries, especially toward the centre of the areas, contain large numbers of these leucocytes, some of which have even wandered into the dead cells. No bacilli were found on sections.

Experiment No. 2, May 19, 1891, 10 a. m.—Small black rabbit; mesenteric vein injected with 0.2 c.cm. of a four days' old culture in plain bouillon. The animal appeared almost overwhelmed by the toxic effects of the injection and died at the end of twenty-three hours. Autopsy made after death: no peritonitis; stomach almost empty; small intestine contains a small quantity of fluid fæces; mucous membrane not injected; no enlargement of Peyer's patches or solitary glands; cæcum and large intestine contained a small quantity of hardened fæcal matter; the liver darkly congested and shows characteristic psorosperm nodules; no areas of necrosis apparent to the naked eye, either on the surface or on section; spleen slightly enlarged and dark; kidneys normal; no cover-slips were made; frozen sections of liver show marked fatty infiltration of the periphery of all the lobules; no necrosis discoverable except those containing coccidia; gelatin plates from liver, spleen and kidneys each give numerous colonies of typhoid bacilli; hardened sections of the liver do not show necrotic areas. Although Experiment No. 2 was negative, as far as regards the finding of necrotic areas, it is worth mentioning that a culture of the typhoid bacillus was obtained from the blood in the foregoing cases at the end of forty-eight and twenty-three hours respectively.

Experiment No. 3, June 24, 1891, 4 p. m.—Medium sized rabbit; mesenteric vein injected with a 0.3 c.cm. of a twenty-six hours' old culture in plain bouillon. Animal killed June 29, 1891, 4 p. m. (at the end of five days). No peritonitis; stomach distended with food; spleen much enlarged, dark red; kidneys normal; liver contains a few coccidia nodules; no other areas of necrosis to be observed; frozen sections of the liver appeared to be normal in all respects, except the presence of coccidia above noted; small intestine contains a medium amount of fluid, yellowish fæces; mucous membrane of ileum uniformly congested and extending up the gut to the distance of 14 inches; above the ileo-cæcal valve there are to be seen eleven well-marked ulcerations; the largest ulcer involves an entire Peyer's patch and measures 14 by 21 millimetres; the others are small roundish oval ulcers and involve the solitary follicles; all of them contain a central slough, the necrotic process extending in several down to the peritoneal coat of the bowel; all have overhanging edges and show a distinct margin of congestion; large intestine normal; the mesenteric glands distinctly enlarged, and several show upon the surface, and upon section, small yellowish areas of necrosis; cultures from right ventricle, liver, spleen, mesenteric glands, and kidneys; the plates from liver and spleen show numerous colonies of typhoid bacillus, while those from the blood, mesenteric glands, and kidneys give a few colonies of staphylococcus citreus; hardened sections of the mesenteric glands and of the spleen give characteristic caseous areas of tuberculosis; numerous tubercle bacilli found on stained sections; hardened sections of liver normal; sections of the intestinal ulcers show, microscopically, a central necrosis extending down to and involving the peritoneal coat; this necrosis, in each instance, is densely surrounded by an area of polynuclear leucocytes; outside of these were seen a few epithelioid cells in the submucosa; repeated examinations of stained sections of the ulcers failed to discover any tubercle bacilli whatever. With regard to Experiment No. 3, although the microscopical examination proved that the mesenteric glands were tuberculous, the latter condition was definitely excluded from the process, as seen in the intestinal ulcers. The absence of tubercle bacilli in these, the presence of a central area of necrosis surrounded by crowds of polynuclear leucocytes, the involvement of Peyer's patches and solitary glands in the ulcerative process, would, we think, bear out the latter statement.

Experiment No. 6, July 2, 1891, 10 a. m.—Medium sized rabbit; 0.2 c.cm. of a twenty-four hours' culture in 1 per cent. sugar bouillon injected into the mesenteric vein. Animal killed July 7th, 5 p. m. (three days, seven hours); stomach distended with food; small and large intestine normal; spleen not enlarged; kidneys normal; no necrotic areas found in the liver either on frozen or hardened sections; cultures from the blood negative; those from the bile, liver and spleen give numerous colonies of typhoid bacilli.

Experiment No. 7, July 24, 1891, 4 p. m.—Large black rabbit; 0.5 c.cm. of a thirty-six hours' culture in 1 per cent. sugar bouillon injected into mesenteric vein; after recovery from the anæsthetic the animal showed symptoms of acute toxæmia; remained lying on its side with marked tremor of extremities for more than twelve hours; this passed off during the second day; July 29th, 4 p. m. (five days), animal killed; no peritonitis; stomach contains moderate amount of food; small and large intestine normal; spleen much enlarged, estimated to be three times its normal size, dark purplish-red, firm; kidneys normal; liver presents within its parenchyma, immediately beneath the walls of the gall bladder, numerous yellowish-white, roundish necroses; walls of gall bladder much thickened; bile pale, watery, non-viscid, and contains many minute yellowish floating particles; hanging drop made from bile shows a large number of highly motile rods, corresponding in size to the typhoid bacillus; cover-slips from the various organs negative; gelatin plates from bile, spleen and liver give numerous typhoid colonies; plates from the blood and kidneys negative; microscopical examination of hardened sections of liver extending through the wall of the gall bladder show distinct necrosis of the mucous membrane of the gall bladder, with loss of substance, and in the parenchyma of the liver proper many small and large necroses involving the liver cells; these areas stained brightly with eosin; within the capillaries of several of the areas there are seen many polynuclear leucocytes; one such necrosis occupies almost an entire lobule.

Experiment No. 8, August 14, 1891, 9.30 a. m.—Large white rabbit; mesenteric vein injected with 0.4 c.cm. of a twenty days' old culture in 1 per cent. plain bouillon; August 21, 1891, 9.30 a. m. (seven days) animal killed; no peritonitis; stomach, large and small intestines presented nothing worthy of remark; spleen slightly enlarged, dark red; kidneys normal; liver presents, beneath its capsule and on section, numerous minute, yellowish-white necroses; bile green and viscid; cultures from blood, bile, liver, kidneys and spleen positive; frozen section of liver show many necroses, consisting largely of fatty granular liver cells; hardened sections of the liver show necroses, both large and small, resembling in all respects those found in the human liver of typhoid fever.

Experiment No. 11, August 31st, 1891, 4 p. m.—Large rabbit; injection into mesenteric vein .5 c.cm. of twenty-four hours' old culture in plain bouillon; no symptoms of acute toxæmia. September 4th, 10 a. m. (four days after injection), animal killed. No peritonitis; stomach and intestines normal; spleen not enlarged; kidneys normal; liver, numerous very small, round, yellowish necroses under capsule on the upper and lower surface and on section; bile green, viscid; cover-slips from the organs negative; gelatin plates from blood, liver, spleen and kidneys negative; plates from bile contained numerous typhoid colonies; frozen sections from liver showed diffuse fatty degeneration of liver cells and many small necrotic foci; hardened sections gave most characteristic foci of cell death, and there was seen within a branch of the portal vein an extensive thrombus.

Experiment No. 12, August 31st, 1891, 5 p. m.—Large rabbit; 5 cc. plain bouillon culture, twenty-four hours old, injected into mesenteric vein; killed September 13th, 1891 (fourteen days after injection); no peritonitis; spleen dark red and much enlarged; stomach and intestines normal; kidneys very pale on section; striation well marked; liver, numerous minute, sharply defined, yellowish-white areas under capsule and scattered through the liver parenchyma; frozen sections show diffuse, fatty degeneration of liver cells, and well-defined areas of necrosis; frozen sections of kidney show marked fatty degeneration of the epithelium of both the convoluted and straight tubes; cultures from blood and kidney negative; liver, spleen and bile plates give numerous typhoid colonies; hardened sections of liver show many characteristic areas of cell necrosis.

Of the ten rabbits, into the mesenteric vein of which pure cultures of typhoid bacillus were injected, five gave positive results—that is, following this injection at intervals varying from two to fourteen days, the animals were killed, and upon examination of the liver there were discovered well-defined, localized areas of cell necrosis.

Taken in connection with the localized lesions found in the liver of typhoid fever in man the changes brought about in the rabbit's liver are particularly instructive; for, although in the former it could not be positively determined just how much the presence of the bacillus coli communis contributed to the production of these necroses, we have obtained, in the latter, lesions in all respects identical with those found in the human liver by the injection of pure cultures of the typhoid bacillus, and where any action of the colon bacillus could be certainly excluded. The inference would appear to be a legitimate one that the typhoid bacillus is quite capable of producing the areas of necrosis which are so marked a feature in the human liver.

As in the human liver, so likewise in the rabbit's liver we find the essential lesion to be, first, a necrosis of the cells proper of the organ in localized areas, varying in size from a few cells up to an entire lobule, followed by the accumulation of polynuclear leucocytes within the capillaries of the area and their subsequent migration into the dead cells.

With regard to the relation of the bacilli to the experimentally-produced areas of necrosis, we have not succeeded in finding any bacilli present in the areas; nor have we found colonies of the bacilli on section of the rabbit's liver. Our experience has in this accorded with other workers in this line. The explanation for the failure to find the bacilli on section is most probably due to the fact that the tissues were subjected to the influence of hardening agents immediately after the animals had been killed. As is well known, Fränkel and Simmonds have shown that by keeping the spleen and liver of rabbits which have been inoculated with typhoid bacilli for periods varying from twenty-four hours to three or more days, especially at thermostat temperature, the bacilli rapidly multiply, so that, whereas, immediately after the death of the rabbit it was with much difficulty that they could be found; at a later time numerous colonies were to be seen on sections of both liver and spleen. Bearing this in mind, it may be allowable to suppose that many of the colonies of typhoid bacilli found on section in the human liver have developed between the death of the patient and the time of subjecting the tissues to preservative agents. This may account for the fact that so many of the colonies are seen to be surrounded by apparently quite healthy liver cells.

To briefly summarize, then, the results of our study of the lesions found in the human liver following upon an attack of typhoid fever, we believe that we may draw the following conclusions:

1. That the term "lymphoid nodule," by which these localized lesions of the liver in typhoid fever have been heretofore generally designated, is an improper one, since it expresses an erroneous idea as to the origin of these peculiar formations.

2. That these so-called lymphomata are not composed of lymphoid cells, as the term would imply, which have wandered in from the portal vessels, but that, on the contrary, these foci represent well-defined areas of cell-death.

3. That in the earlier stages of the necrosis the nuclei which are found in such abundance in these areas are not the nuclei of lymphoid cells (Orth, Hoffman, Siredey), nor do they arise from the multiplication of the nulcei of the hepatic cells (Wagner, Hoffman), but owe their origin in small part to the disintegration of the nuclei of the liver cells involved, and in greater part to the presence of polynuclear leucocytes which have wandered into the necrotic area.

4. That at a later stage of the process, when the liver cells have become quite broken down into granular detritus, the numerous small, round, and sometimes spindled-shaped nuclei which are observed along the margins of the area, or seen to have penetrated into its centre, are those derived from the connective tissue stroma of the organ (Wagner, Handford).

5. That thus it is probable that the areas of necrosis are replaced by well-defined areas of localized connective tissue.

6. That necrotic areas, resembling in all respects those found in the human liver in typhoid fever, can be reproduced experimentally in the rabbit's liver by the injection into the mesenteric vein of a pure culture of the typhoid bacillus.

7. That although these areas of necrosis in the liver owe their origin to the action of the typhoid bacillus, it has not been possible to more definitely determine in what way this cell death is brought about—that is to say, whether it is due to the immediate presence of the bacilli within the areas of necrosis, or is caused by the action of the so-called toxalbumins which are assumed to be present in the general circulation. It would seem reasonable to suppose that the latter explanation is the more probable, since it is possible to produce well-defined areas of necrosis in the liver of guinea-pigs by the injection of toxalbumins alone, as has been done by Welch and Flexner * in diphtheria, and more recently by Flexner † by means of minute injections of ricin and abrin.

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* Johns Hopkins Hospital Bulletin, 1892, Vol. III, No. 20.

† "The Pathologic Changes Caused by Certain So-called Toxalbumins," Medical News, August 4, 1894.

In conclusion, we desire to express our warmest thanks to Professor Welch, of the Johns Hopkins University, and Professor Councilman, now of Harvard University, for the valuable suggestions made from time to time during the progress of this investigation, and to state that the success attending the experimental work was largely due to their kind advice and assistance.

VII.—NEURITIS DURING AND AFTER TYPHOID FEVER.*

BY WILLIAM OSLER, M. D.

Any reference to the literature of paralysis in typhoid fever is superfluous since the appearance of the treatise by Ross and Bury on *Peripheral Neuritis* (London, 1893), in which the last named author has given a very full account of the subject, with a copious bibliography. He states, however, that "the conviction has indeed been forced upon our minds that the material for the induction of positive conclusions with regard to the relation between typhoid fever and the continued fevers generally and multiple neuritis does not at present exist, and that the doctrine can only be placed on a secure basis by new and carefully recorded observations."

I propose in this paper to give an account of the cases which have come under observation during the six years (to May 15th, 1895) in which the Johns Hopkins Hospital has been open.

They may be grouped into instances of local neuritis and of widespread, diffuse, multiple neuritis.

LOCAL NEURITIS.

Among 389 cases under treatment there have been four with well-defined symptoms of local neuritis, and there is a dispensary case which was not treated for the fever in the Hospital.

Before describing these, I would like to call attention to a very interesting and distressing affection which must also, I think, be classed as a neuritis—namely, the *tender toes* of typhoid fever.

When in the Report on Typhoid Fever, issued in 1894 (Vol. IV), I called attention to this symptom, I had not seen any mention of the subject in the literature; but in Ross and Bury's monograph there is a reference to a paper by Handford, which I had overlooked, in which this feature is accurately described. His words are: "For some weeks past there has been tenderness of the toes of both feet, so that the toe-nails could not be cut on account of the pain it caused in the nail-bed and in the pulp at the end of the toes. In three other cases recently," he says, "I have met with this condition of pain in the toes, and in one of them in the arms also. In one instance the tenderness of the feet was so great that they had to be protected from the pressure of the bed-clothes by a cradle. But in none of them was it followed by muscular wasting or definite loss of sensation so far as I could detect."

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* Read before the Neurological Society of Philadelphia.

Not having met with the condition before using the baths, I was inclined to regard it as an effect of the cold water; but in a personal communication from Dr. Handford I gather that his cases were not treated by the Brand method, so that it is evidently one of these coincidences which are so apt to be misleading in medicine. Before July, 1890, when the Brand method was introduced into my wards, I had never seen an instance. Since then we have had twenty or more cases, all of which have been bathed.

Though not serious, the condition is very distressing, and a cause of much suffering. It usually develops in the latter half of the disease; sometimes, indeed, after the temperature has reached normal; thus, in a patient at present in ward C, the tender toes were not noticed until early last week, the fourth of the fever, and when the temperature had already begun to fall. The patients usually complain first of the pressure of the bed-clothes, and as Dr. Handford mentions the sensitiveness is so great that the toes have to be protected by the use of a cradle. The area involved has been in all of my cases the toes, with occasionally the pad of the sole of the foot; never the dorsum, and rarely extending as far back as the heel. The tenderness has always seemed greatest at the tips and on the plantar surface of the toes. Even the slightest pressure on the nail causes pain. I have never seen any redness or swelling, though of course in the reaction following the cold baths it is not uncommon to see the feet extremely red. In a few instances there has been sweating confined to the feet and toes.

At first I thought that the pain might be caused by the pressure on the sensitive corium of dry and hard layers of the cuticle macerated by repeated immersions, but the skin has always looked natural, and several of the worst cases have been those which have had only a few baths.

The pain persists for a variable period, from a few days to ten days. In no instance has there been any motor disturbance, and in no case has there appeared to be any loss of power in the muscles of the toes after convalescence was established. The cases have all recovered, and we have been led gradually to regard the condition as one of acro-paræsthesia possibly due to neuritis.

The treatment is not very satisfactory. We have used all sorts of applications; the one which seems to give most relief is a hot cocaine solution on cotton wool.

Local neuritis in typhoid fever may occur either at the height of the disease or after convalescence has been established. It may prove serious and lead to great wasting of the muscles, or it may pass away rapidly after an acute attack.

The two following cases are the only ones I have met with in which the neuritis developed during the height of the fever:

CASE I.—*In second week severe neuralgic pains in arms; great tenderness of the muscles; numbness of hands; no arthritis; no sensitiveness of nerve trunks. Recovery without wasting.*

C. W., aged 25, admitted October 8, 1890. Patient had a moderately severe attack, and the temperature did not reach normal until the 27th day. On October 18th, that is on the 14th day of the fever and while the temperature ranged between 102° and 103°, she began to complain of pains in the arms. She had not had a cold bath since the tenth day, October 14th. The pains were neuralgic in character. On the 19th the note reads: "This morning pain is very much worse, she can scarcely lift the arms. There is no swelling of the joints or any tenderness about them on the firmest pressure. The soreness is particularly in the muscles. She winces at once when they are grasped. The biceps is particularly tender. There is no swelling of the ulnar nerves, no soreness in the brachial plexuses in the axillæ or above the clavicles. The pain to-day is not shooting in character, but it extends down to the fingers. There is no numbness. The pain is so severe that the arms are kept on a pillow and she is quite unable to move them." On the 20th the note reads: "Soreness persists. Cannot lift the arms; fingers can be moved. The pain is continuous. There is no disturbance of sensation, no pins and needles, no swelling of the joints; the legs are not painful." On the 22nd the note reads: "The hot applications have relieved the pain somewhat. Yesterday the hands were quite numb. She says the hands ache like toothache. Joints not swollen; arms and forearms still very sore to touch." From the 18th to the 30th this condition persisted with very little change. She had lead and opium applications and antipyrin internally. The temperature meanwhile gradually fell and her general condition improved. On November 2nd the note is: "Arms very much better; pains still in the left arm and she can move the arms well; no wasting of the muscles." Within the next two weeks she improved very rapidly; the pains in the arms gradually disappeared, and she recovered completely without any wasting of the muscles. The pain in this case was of a most aggravated character, sometimes causing the patient to cry out.

CASE II.—*In third week onset of severe pains in right arm and leg; rapid improvement in arm; agonizing pain in leg; great sensitiveness of muscles; erythema nodosum; recovery after ten days.*

Mary McG., aged 13 (Hos. No. 6405), admitted December 4, 1892, about the end of the second week of what proved to be a very severe attack of typhoid fever. The temperature kept up for an unusually long time, and she became so feeble that after the 44th bath they were discontinued. It was not until the end of the 5th and throughout the 6th week that the temperature fell to normal. On December 14th, while the temperature was still high, having been constantly for several days in the vicinity of 105°, and after she had been sponged with ice-water for two days, she began to complain of very great pain in the right arm and in the right leg, of such severity that she cried out constantly and she had to have morphia. These attacks continued between the 14th and the 20th with great severity. In the right arm the pain soon subsided; there was no involvement of the joints; no pain along the nerve trunks. She screamed out if any attempt was made to move the right leg. There was no tenderness about the hip, no swelling of the knees, and repeated examinations seemed definitely to exclude any articular trouble. Grasping the leg at any place seemed to cause extreme pain. The leg was not swollen.

On the 18th three patches, like erythema nodosum, appeared on the right foot, one at the metatarsal joint of the small toe, one midway between the heel and toes, and one on the outer and back part of the heel. They looked like large chilblains, and around one there was a distinct bluish discoloration. The two smaller ones disappeared within a day or two. The larger one on the heel remained red for some days. There was no superficial necrosis. She never seemed able to localize the pain accurately. It was never definitely in the situation of the sciatic nerve. It was quite uncontrollable by anything but morphia. After causing great anxiety to us, and distress to the patient, for nearly ten days, the pain subsided and had disappeared by the 25th or 26th, two weeks at least before the temperature became normal.

In these cases pain was the dominant symptom, and there was extreme sensitiveness on pressure, particularly over the muscles. There was neither arthritis nor thrombosis, and in *Case I*, as there was numbness and tingling in the fingers and hands, it seems more reasonable to refer the condition to a neuritis than to myositis. The second case presented the peculiar lesion of an erythema nodosum, which I have seen also in a case of alcoholic neuritis.

There are cases in which the patient, when convalescent, complains of soreness of the muscles and of exquisite tenderness when they are touched. So far as this latter feature is concerned, it is, of course, very common in peripheral neuritis, particularly in the alcoholic form; but the muscle soreness may be present without any trace of involvement of the nerves. (See note on *tender legs* at page 316.)

CASE III.—*Pain in left leg; sensitiveness in nerve trunks; soreness in tibialis anticus; rapid recovery.*

John M., aged 27 (Hos. No. 4171), admitted November 4th, 1891, on the 10th day of a mild attack. On the 25th of November, when he had been already convalescent more than 10 days, he complained of very severe pain in the front and back of the left leg, which came on suddenly. There was distinct sensitiveness over the nerve trunks, the posterior tibial, and the peroneal, and also along the tibialis anticus muscle. The toes were also sensitive and there was a dulling of sensation in them. Throughout the 26th this condition persisted and it seemed probable the patient was going to have a severe post-typhoid neuritis, but on the 27th he was very much better. There was no tenderness, and the sensitiveness in the anterior tibial muscles had disappeared.

CASE IV.—*With onset of convalescence soreness and pains in limbs, particularly the arms; 'pins and needles' in left foot; swelling and tenderness of left arm; gradual improvement and recovery without atrophy.*

Wm. McM., aged 32 (Hos. No. 6329), admitted November 19th, 1892, at about the second week. The attack was of moderate severity, the temperature ranging between 103° and 104.5°, and not falling to normal until the fifth week. Just about the time the temperature became normal, that is on the 12th of December, the patient complained of general soreness and pains in the limbs, particularly in the arms, and he winced on pressure upon the forearms and arms. He had been in very good condition and convalescence seemed well established. The grasp of both hands seemed weak, but particularly the left, and he complained of a sensation of pins and needles in the left foot. There was no tenderness along the nerve trunks; no pain on pressure on the muscles of the calves; he winced a little when the muscles on the right thigh were pressed. On the 17th of December the note reads: "Left arm looks somewhat swollen and feels tense. It is not red; the temperature is not elevated. He moves the muscles with difficulty and says the arm is very sore. On the inner part of the upper arm there is very great tenderness along the course of the brachial artery and of the nerve trunks. The ulnar nerve is also somewhat tender at the elbow. There is tenderness of the muscles, particularly of the biceps and of the extensors of the upper arm. There is no anæsthesia; no sensation of pins and needles. All movements in the limb cause him pain. There are flying pains in the legs, but no swelling; no tenderness; knee jerks were increased; no ankle clonus." The swelling and tenderness in the left arm gradually disappeared within ten days and there was no wasting of the muscles.

In both of these cases there was great sensitiveness of the nerve trunks, and in Case IV it seemed for a time as though the patient were about to have an attack of multiple neuritis, but the symptoms became localized in the left arm, which became swollen and exquisitely tender.

CASE V.—*Severe fever five months ago; pain in the right foot during convalescence; gradual atrophy of the leg muscles; foot-drop; gradual recovery.*

Michael E., aged six years, applied at the Neurological Department of the Dispensary on January 19th, 1895, complaining of difficulty in walking and pain in the right leg. He is the sixth of six children. The family history is good.

He has always been a very active and strong child. He has had measles and mumps.

Five months ago the patient was taken ill with fever, and evidently had a very severe attack, as the father said, "he was expected to die every day." He was delirious, but had no diarrhœa. An elder brother had the disease about the same time, said to be typhoid, and died.

After persisting for about six weeks the fever left and he began to improve. He had some difficulty in speaking during convalescence. Nothing further was noticed until he got well enough to sit up, when he complained very much of the right foot, saying that it was painful, and he could not put on his shoes. The foot felt cold and was evidently very sensitive. He would not let anybody touch it, and he could not walk upon it. This gradually improved, and has been able to get about on it with a limp.

Present Condition.—The child is pale, but fairly well-nourished. The intelligence is good. The muscles of face, arms, and of the body seem perfectly normal. In walking the right leg is flexed at the knee. The foot is held limp, the toes bending down, and the foot is slapped on the floor. The act of walking does not seem to give any pain. On examination the right leg below the knee is decidedly smaller than the left. He has foot-drop and no voluntary power in any of the muscles below the knee. It is difficult to make a proper examination, as he cried out, and scarcely will allow the leg to be touched, but this is apparently more due to nervousness than to actual pain. There is well-marked reaction of degeneration in the muscles of the lower leg.

Instances of local paralysis of this kind following typhoid fever are not very uncommon, and a number of references are to be seen in Bury's article.

This localized atrophic paralysis after typhoid may be due to polio-myelitis, and the distinction between the central and peripheral nature of some of the cases is often very obscure. Sudden onset, sensory disturbance, and permanent disability in certain of the muscles of the affected limb, speak for a central lesion. The case reported by Shore (St. Bartholomew's Hospital Reports, Vol. XXIII), is perhaps the most satisfactory on record, as showing conclusively the existence of acute polio-myelitis in connection with the atrophic paralysis following typhoid fever. In Case V, while the general appearance of the limb, as the boy stands, is highly suggestive of spinal paralysis, yet the gradual onset and the extreme sensitiveness are in favor of neuritis. The reaction of degeneration and the absence of the reflexes are symptoms common to both central and peripheral lesions. For the third and most important diagnostic criterion; viz.: the complete recovery or permanent disability in certain muscles, the time which has elapsed has not been sufficient.

MULTIPLE NEURITIS.

The most serious forms of paralysis following typhoid fever are those in which there is a rapid or gradual development of paralysis of the legs or of both arms and legs. Cases of the paraplegic type are not infrequent in the literature. In my own practice I have, however, never met with an instance. Widespread loss of power in all four extremities is, if one may judge from the recorded cases, very much less common; but within the past two years the following cases have been under my observation.

CASE VI.—*Severe fever of three weeks' duration; during convalescence weakness of arms and legs, with finally complete paralysis; foot-drop and wrist-drop; great soreness of the muscles; progressive improvement; complete recovery, after persisting for more than a year.*

D. S., male, aged 9, applied at the Neurological Department of the Dispensary November 1st, 1893, with paralysis of arms and legs.

There is nothing of any moment in his family history.

He was always healthy as a child. He went to school last winter and developed well in every way. Last July he was in bed three weeks with a fever, said to be malaria, but from the mother's description and from the length of time he was in bed there can be but little question that it was typhoid fever. During convalescence from the illness it was noticed that he did not use his arms and legs freely. The mother thinks that this came on gradually, and she thought at first that it was due entirely to weakness from the prolonged illness. He has not walked since he was put to bed with the fever. The arms have been gradually growing weaker, and two weeks ago he lost power in them altogether. He has never complained of any pain. The speech has not been affected. From the statements of the mother there was evidently a progressive loss of power in both arms and legs.

The notes which Dr. H. M. Thomas took at his first visit are briefly as follows:—

The boy is bright and intelligent-looking. The eyes are steady, freely movable, react to light and on accommodation. The muscles of the face and tongue act normally. The muscles moving the head act well. The shoulder-girdle muscles act voluntarily with a fair amount of strength. The deltoids act well. Flexion and extension at elbow-joint are somewhat weak on both sides. The supinator longus does not act on either side. Below the elbows there is scarcely any power. The hands are in typical wrist-drop position and cannot be extended in the least. He is just able to flex the two middle fingers on the right side and the fore and middle fingers on the left. There are no movements of the smaller muscles of the hands. The whole arm and fore-arm are very thin. The sensation is quite normal. The skin over the last phalanges is a little smooth. When sitting on the edge of the table the back is bowed and he cannot sit straight. When on the back the patient can flex both legs on the body to an angle of about 45°; the left slightly stronger than the right. He has some power in extensors and abductors. He can rotate the legs in and out. The extensor muscles of the knee are weak on both sides; the flexors are the weaker. Below the knees there is almost complete paralysis. He can slightly flex the toes. Both legs are markedly atrophied. In grasping the calf muscles the patient shows signs of pain, also winces on pressure over the sciatic. The muscles of the forearm also are slightly painful on pressure. The knee jerks cannot be obtained. The muscles do not react to faradism, and react very slightly to the galvanic current. The patient was ordered the syrup of the iodide of iron, m. xv three times a day, and massage with electricity.

On January 12th, 1894, the note reads: "He has been given electricity three times a week, and has improved. He can now walk a little alone. He has a very typical 'steppage' gait. There is still complete foot-drop. The muscle groups are still sensitive on firm pressure. There is still the reaction of degeneration in the muscles below the knees. The muscular strength in the arms has improved very much. He can flex the wrists with a fair amount of power."

Throughout the early part of the year the boy did very well, and there was a progressive improvement.

He came to the Dispensary on the 24th of August, when it was noted that, though he still drags the toes somewhat, the gait has lost its typical character. He can move all the muscles of both arms and legs, and has considerable power. All the muscles respond quickly to the electrical tests.

On December 1st Dr. Thomas made the following note: "Legs are well-nourished, and he moves them in every direction; he can flex the legs and thighs flat to the body, and resists extension very well. The flexors of the knee are strong, but not so strong as the extensors. When the foot is extended it cannot be dorsally flexed; when raised, however, it can be easily extended. In the arms all the muscles act normally, but the flexors are stronger than the extensors. This is especially true of the wrist. The muscles of the legs respond to the faradic current; the flexors respond to a third higher current than the extensors. They also respond to the galvanic. The extensor and flexor muscles of the arm respond promptly. Sitting the boy still has a tendency to bowing of the back and to toe-drop."

I showed this boy at one of my clinics in January, 1895, when he seemed well in every respect, and the only abnormality to be detected was an inability to raise himself readily on his heels or on his toes.

CASE VII.—*Severe attack of typhoid fever; during convalescence progressive loss of power in arms and legs; recovery in arms; atrophy of leg muscles with foot-drop; great improvement.*

Wm. E. K., aged 24, admitted October 16th, 1893, complaining of inability to walk.

The family history is good. The father and mother, and one brother and three sisters are living and well.

He has had the usual diseases of childhood; he has not used alcohol to excess; and has never had venereal disease. In August, 1892, he had a very severe attack of typhoid fever of eight weeks' duration, with much delirium, and with a pulmonary complication; and I am indebted to Dr. A. O. Scott, of Fairfield, Pa., for a description of the original disease. During convalescence it was noticed that the limbs became gradually weak and there was a progressive loss of power in the hands and in the legs. The double wrist-drop persisted for some months, and gradually disappeared. He was for a long time bedridden, and it was not until May of this year (1893) that he was able to get up, and begin to use crutches. He did not remember that he had had much pain with the attack, but there was some swelling of the feet. During the present year the power has been improving slowly in the legs, but it has been interrupted by the development of severe paronychia in both big toes. The hands and arms recovered power completely.

Condition on admission.—The patient is a healthy looking man; walks with crutches. He has no fever. The mental condition is good and he gives a very clear account of the history of his case. He looks a little pale; the pupils are equal and react to light and on accommodation.

The examination of the abdominal and thoracic organs is entirely negative. A point of interest, however, is the fact that his peripheral arteries are readily palpable.

The muscles of the face acted normally; there was slight wasting in the arms, but all the movements were readily made. The deltoids appeared to be weaker than the other muscles, and the extensors in the arms were weaker than the flexors. The extensors of the left hand were not quite as strong as those of the right. There was marked wasting in the muscles of the lower extremities, with bilateral foot-drop. Corresponding to this there is general loss of muscular power. The legs could be flexed and extended upon the thighs, and the thighs flexed upon the abdomen quite readily, and this even when the patient was trying to resist. The greatest atrophy and the most marked loss of power is in the extensors of the feet. He cannot flex the foot at the ankle at all, nor are the movements of inversion and eversion possible. Sensation does not appear to be impaired in any way. He distinguishes readily everywhere the head from the point of the pin, with the exception, perhaps, in the left leg, where there seems to be a little dulness; he distinguishes heat from cold. The knee jerks could not be obtained; ankle clonus was not present. The reflexes in the arms are present, and are active. There was reaction of degeneration in the atrophied muscles. There is no involvement of the bladder or of the rectum. The patient was given persistent massage and a strychnia tonic. The big toes were first operated upon for the condition of paronychia, and they healed readily. The patient remained under observation nearly six months and improved in every way. By the middle of December the power seemed fully restored in the arms and hands. The deep reflexes were still a little increased. The patellar reflexes had not returned. The extensor muscles of the feet had not yet regained their full power, but both feet could be flexed somewhat. The patient had a typical steppage gait of foot-drop. Throughout the early part of the year he did remarkably well, gained in strength and could get about readily without crutches. He left the hospital May 9th very greatly improved in every way. I heard of the patient through Dr. Scott, on January 16th, 1895, who said that the progress continued satisfactorily.

CASE VIII.—*Fever of four weeks' duration; numbness in legs; sudden onset of paralysis in arms and legs; gradual improvement in arms; slight in legs, in which the paralysis recurred; marked improvement under treatment.*

Stephen T. McK., aged 25, admitted November 4th, 1894, complaining of loss of power in both legs, weakness in the hands, and pain in the lower part of the back.

His parents are dead; the father of bilious colic; the mother of pneumonia. He has two brothers and one sister living and well; there have been no nervous troubles in his family.

The patient had measles and whooping cough as a child, and pneumonia when thirteen. In June, 1892, he had typhoid fever, and was confined to the house for seven weeks. He had gonorrhœa three years ago.

Present illness.—In February, 1894, the patient had a protracted fever, which lasted four weeks. He had vomiting; no diarrhœa; no convulsions. He had some sweating; no chills. He had pain in the back and legs. It was thought by his physicians to be typhoid fever or typho-malarial fever.

Early in the disease he had numb feelings in his legs, but the trouble from which he is now suffering did not begin until convalescence. He had been up and about, and sitting in a chair for a while each day when he suddenly lost power in the upper and lower extremities, below the elbows and knees. He had a sensation of pins and needles. There was no paralysis of the tongue, or of the facial muscles, and no trouble with the sphincters. He is quite positive that the feeling of numbness preceded the loss of power which he insists came on in the course of a day.

After the onset of the paralysis the patient continued to sit up in a chair each day, and he noticed that his feet would swell after they had been hanging down for any length of time. There was also, he says, loss of sensation.

In May he began to notice some improvement in the condition of the arms. The sensation gradually returned and then the muscular power. About the latter part of May he was able to feed himself.

The sensation in the feet recovered first, and then gradually the muscular power. Through the months of June and July he was under treatment in Washington, and was able to get about with the use of the stick. He went home, and about four weeks later lost again the power of using the legs, but had no disturbance of sensation. Since then he has begun to recover; he can move the feet slightly, but is still unable to walk.

Present condition.—The patient is a poorly nourished man; looks a little pale; the tongue is clean. The intelligence is good; he talks clearly and well. There is no involvement of the facial muscles; the pupils are equal and the iris reflexes are present.

The examination of the abdominal and thoracic organs is negative. There is no enlargement of the spleen. The trunk muscles look well-nourished; the spine is straight, and there is no tenderness. The hands look thin, but there is no special wasting of interossei or thumb muscles. All the movements are perfect, and the power in the fingers and the grasp of the hands are good. These muscles seem to have recovered completely, though he says he is not nearly so strong as he was.

The legs are very thin, particularly below the knees. All of the muscles are here very much wasted. The legs can be moved freely at the hips and at the knees. There is complete foot-drop. The patient can neither move the feet nor the toes. The knee jerks are absent; there is no ankle clonus; no œdema; the feet feel cold. There are no fibrillary twitchings. The sensation is everywhere perfect to heat and cold. The electrical tests show the reaction of degeneration in the peroneal nerves; the extensors cannot be made to act at all. The gastrocnemius and soleus show marked reaction of degeneration. The arm muscles react well to weak currents.

Patient was ordered strychnia and massage to the legs twice daily.

Throughout November and December the patient improved rapidly. He was soon able to walk with a stick. The feet have perspired a great deal, and they get very red after he has walked about on them. The gait had the typical steppage character of extensor paralysis.

By the first of January he could walk without a cane. On November 18th he weighed 102 pounds; he gained rapidly, and on December 10th he weighed 118 pounds, and on his discharge, January 28th, 135 pounds. His improvement was satisfactory and progressive.

On December 4th the electrical reactions were as follows: (Dr. Oppenheimer.)

Arms.—All muscles and nerves react well to moderate currents.

Legs.—The peroneal nerve of right leg reacts well to moderately high faradic current; contraction slow, but does not give the typical reaction of degeneration which it did on previous occasions. Muscles of the right leg do not react. In the left leg the contraction of the peroneal is slower and lazier than that of the right. The muscles do not react.

To the galvanic current the peroneal nerve and the muscles react, and there is a sharp contraction, not particularly slow.

At the time of discharge he had gained 33 pounds; he still had the characteristic gait of extensor paralysis. He had not regained much power over the muscles of the toes. He could flex and extend the great toe of the right foot only. On the left side he could move the toes a little better. He could flex and extend both feet, and abduct and adduct, but not to the full extent. The legs at the middle of the calf had gained greatly in circumference.

CASE IX.—*Severe attack of typhoid fever; in third week soreness in legs; gradual paralysis of arms and legs; on admission feebleness of arm muscles; foot-drop; wasting of muscles of legs; great muscular soreness; improvement.*

George R., aged 10, admitted November 19th, 1894, complaining of weakness in the arms and legs, and tingling sensations in the fingers.

Family history.—Father and mother, and one sister living, and healthy.

The patient had measles when he was five years old; since then he has been very healthy up to the onset of the present illness.

On September 26th he was attacked with typhoid fever; and was in bed for seven weeks. It was evidently, from his father's statement, a very severe attack, as he was delirious and had high fever. About the end of the third week of his illness he began to complain of stiffness and soreness in the thighs and calves, which was noticed by his father in moving him about in bed. The feet felt cold, but there was no complaint of numbness, or of feelings of pins and needles. A week after the beginning of these symptoms the patient was unable to support himself, and on attempting to walk would throw the foot forward and bring it down heavily on the floor. At this time he could not move the feet or toes.

Two weeks after the legs were affected, the arms and hands became weak. It was at first noticed that he could not feed himself properly. He had sensations of pins and needless in the hands and fingers. At no time had he typical wrist-drop. He had no severe pains which caused him to cry out, but he was very tender and would wince when moved. The sphincters were never involved. The condition gradually grew worse until the time of his admission to the hospital.

In the Dispensary, November 13th, the electrical examination showed no reaction of degeneration in the arm muscles, but a well-marked reaction of degeneration in the leg muscles.

Present condition.—On admission the patient is a fairly well-grown lad, but poorly nourished; the lips and mucous membranes are of good color; the pupils are of medium size, equal; the reflexes are normal; the movements of the facial muscles are well performed.

The examination of the abdominal and thoracic organs is negative. The spleen is not enlarged. Both arms and legs look atrophied.

There is no wrist-drop. All movements of the fingers, hands and arms are perfect. The grasp, however, is extremely feeble. There is no sensitiveness along the course of the nerve trunks, but the muscles themselves are very tender. He cries out if the arm is grasped above the wrist. The muscles of the legs look wasted. There is complete foot-drop. He cannot move the toes or the feet. He can flex and extend the legs; he can get out of bed, but stands with a little difficulty, and walks with the aid of a cane, drags the toes, and has a typical steppage gait. The sensation seems perfect, and he no longer complains of pins and needles; there is no tenderness along the course of the sciatic; the sensitiveness of the muscles is very marked. He winces if the thighs or calf muscles are pressed. There has been no trouble with the sphincter muscles.

The patient was under observation until February 4th, 1895; the general condition improved rapidly. On admission he weighed 56 pounds, and at the time of his discharge weighed 65. He recovered power in the hands completely, so that the grasp was quite good. The foot-drop persisted, and he still could not move the toes. There was no power whatever to flex or extend the foot, or to abduct or adduct. The tenderness on pressure had almost completely disappeared. The electrical condition remained about the same; no reaction to the faradic current in the muscles or nerves of the legs.

With the galvanic current there is a typical slow, lazy contraction of the tibialis anticus of both legs.

DIAGNOSIS.—These cases of multiple neuritis were not under observation during the primary illness, and the diagnosis of typhoid fever rests upon the statement either of the physician or of the relatives. The only doubt really is *Case VIII*, as this patient is stated to have had typhoid fever in June of 1892. I have not been able to get any information from the physician who attended him, but his illness was evidently very severe, as he had fever of four weeks' duration, without diarrhœa and without chills, and the paralysis did not come on until convalescence was established. In *Case IX*, in the third week of the illness the father noticed the soreness in the legs.

The mode of the onset is of some importance in the diagnosis, since there are cases of multiple neuritis which set in with fever and in which the symptoms develop with great rapidity, as in *Case VIII.* In illustration, and for the purpose of comparison, I may mention the following instance of multiple neuritis following exposure to cold: A. B., æt. 10, one day about the middle of September, 1894, was exposed to wet and cold, and on the following morning, soon after breakfast, he complained of weakness in the arms and hands. Towards the afternoon his legs became weak, and by night he could not walk. He was put to bed, and had a prolonged illness of a month's duration, with fever and delirium. He became perfectly helpless, but there were never at any time symptoms of typhoid fever. The sphincters were not involved. There was rapid wasting of the extremities. Throughout November and December he improved, and was gradually able to get about.

When admitted on January 2nd, 1895, the condition was as follows: He is a pale, delicate-looking lad; walks with a very distinct steppage gait, flopping the feet down. The muscles of the eyes and of the face act normally. There is no involvement of the pharyngeal muscles. The muscles of the head and neck act well. The shoulders are easily shrugged and resist forcible depression. The depressors of the shoulders also act well. Of the arms the pectoral muscles are strong on both sides. Flexion and extension at the elbows are good on both sides. The muscles of the upper arm and shoulder girdle are feebly developed. In the hands dorsal flexion at the wrist is weak; palmar flexion is also weak, but better than the dorsal flexion. He is entirely unable to extend the fingers at the metacarpo-phalangeal joints. If these joints be passively extended, the patient can slightly extend the terminal phalanges. The grasp of the hand when the wrist is held and flexed dorsally, is poor; better on the right side. The small muscles of both hands are very weak. The patient is not able to oppose the thumb and little finger. The hands are moist and clammy, but there are trophic changes. The legs are thin, particularly below the knees. He can flex and extend the thighs on the abdomen, and the legs on the thighs. There is typical foot-drop. He cannot flex or extend the feet at the ankles, and abduction and adduction of the feet are impossible. There is no power to move the toes. The knee jerks are absent. There is no special sensitiveness anywhere of the nerve trunks, or of the muscles when grasped. There is no reaction of degeneration in the muscles of the shoulder girdle or of the upper arm, or in the supinator in the muscles of the palmar side of the forearm. On the dorsal surface the muscles do not react even with the high faradic current; there is a slow, lazy contraction with the galvanic. The reaction of degeneration is present in the tibialis anticus and the peroneal group of muscles in the legs.

The boy remained under treatment for two months, and improved very much in walking and in the muscular power of the hands, but he still has foot and wrist-drop.

The differential diagnosis is between peripheral neuritis and anterior polio-myelitis, but, as Gowers says, the distinction of a central from a peripheral lesion is often very difficult. The points of importance are as follows:

First. The mode of onset, which in myelitis is very much more rapid. It will be noted that only in Case VIII was the onset stated to be sudden, yet in this very case the complete recovery of the hands, the very striking improvement in the condition of the legs, and particularly the fact of a well-marked relapse leave very little question as to the peripheral nature of the disease.

An additional difficulty in the matter of onset is the fact that there are cases of polio-myelitis anterior which set in sub-acutely, and on the other hand cases of polyneuritis which have really an abrupt onset.

Second. In polio-myelitis the sensory symptoms are quite subsidiary, whereas in polyneuritis there is more or less pain, or sensations of numbness and tingling. It will have been noticed in the report that the muscles themselves were in several cases extremely sensitive to pressure, a point to which Wilks and others have called attention as specially characteristic of neuritis.

Third. The atrophy is certainly more rapid in the central lesion, but it may reach quite as high a grade in neuritis. In *Case VIII* the wasting of the leg muscles when he first came under observation was very pronounced.

Fourth. According to most authors the electrical tests afford very little assistance in the diagnosis, since the reaction of degeneration is present in both, but there is this important difference; a muscle which has lost its faradic contractility in consequence of destruction of the motor cells is permanently damaged, whereas the loss of faradic contractility in the muscles in polyneuritis does not by any means indicate that the lesion is a permanent one, so that always the gradual recovery of the faradic contractility of the muscles is a point which favors the diagnosis of neuritis. Loss of reflexes, trophic changes, girdle sensation, disturbances of the centres in the lumbar region of the cord offer, as a rule, no special points of differentiation. In not one of the four cases of multiple neuritis were there any special psychical changes, which are so common in the alcoholic form, and which, when present, afford really an important aid in diagnosis.

Fifth, and perhaps most important of all, is the subsequent history. Complete recovery is almost the rule in multiple neuritis. In *Case V*, which came under observation November 1st, 1893, with typical wrist and foot-drop, the patient appeared at my clinic a few weeks ago without a trace of paralysis apparent, and the only remnant was shown in an inability to raise himself on his heels or toes. *Case VII*, in which the paralysis and atrophy were very extensive in both arms and legs, I heard of last on January 16th of this year, and it is stated that the paralysis has almost completely disappeared. The other two cases have recovered power in the arms, but still have foot-drop; but the improvement which has been made warrants the belief that they will recover completely. No such complete recovery ever follows an extensive polio-myelitis. Certain muscle groups are sure to remain permanently damaged.

It is important to remember that after typhoid fever there may be a certain amount of weakness of the legs, which never in reality amounts to paraplegia. Sometimes there is with it slight œdema. This usually is a transient affair, which passes off in a few weeks with the full establishment of health. A few months ago I saw a case of typhoid fever with severe hæmorrhage, and during convalescence there was for a time a difficulty in walking which seemed quite out of proportion to the degree of weakness or atrophy of the legs.

PROGNOSIS.—Upon the diagnosis rests entirely the opinion which we can give to the friends as to the future outlook. Death, however, we may say, from polyneuritis, or from any form of paralysis, indeed, after typhoid fever, seems to be excessively rare. As in other forms of multiple neuritis, so in this, the outlook for complete recovery is good; the histories I have given show how favorable is the course, even in very severe cases.

In *treatment* persistent massage is very important; electricity is of less value; medicines are of doubtful utility; from twelve to eighteen months time is the essential factor.

VIII.—POST-TYPHOID BONE LESIONS.

BY HAROLD C. PARSONS, M.D.,
One of the Resident Staff of the Hospital.

(*From the Surgical Department of Professor Halsted.*)

Among the sequelæ of the continued fevers, the lesions of bone have long occupied a place of prominence. In the Toner Lecture, 1876, W. W. Keen quoted forty-one cases, thirty-seven of which had followed typhoid fever. He remarks that "typhoid as usual claims the larger share," inferring that such had been the experience of those before him. In the same year Sir James Paget described most fully, from the clinical standpoint, an inflammatory condition of bone occurring at various periods after typhoid fever, pursuing a more or less chronic course, with but little tendency to spontaneous recovery, except after long periods of time. He had observed some seventy cases, all after typhoid fever.

Prior to these observations, Murchison[*] reported necrosis of femur, tibia, and temporal bone following the same disease, and, later, Affleck described periostitis of humerus in two cases, and of the tibia in another.

Hayward[†] reported several cases, one of which did not go on to necrosis; also one of multiple lesion.

Jackson[‡] observed periostitis of rib with necrosis occurring two months after typhoid fever, with recovery after seven months.

With the identification of the Eberth-Gaffky bacillus as the specific cause of typhoid fever, the nature of these bone lesions has been investigated more thoroughly, with results which have established a relation between them and the primary typhoid attack.

Ebermaier,[‖] in 1887, obtained from two cases of suppurative post-typhoid periostitis the bacillus of Eberth in pure culture. Orloff,[§] in

[*] Continued Fevers of Great Britain, 1873, p. 582.

[†] British Medical Journal, Vol. I, 1885, p. 16.

[‡] British Medical Journal, Vol. I, 1885, p. 428.

[‖] Deutsches Archiv für klin. Med., Bd. XLIV, p. 141.

[§] Centralbl. für Chirurg., May 24, 1889.

1889, in a similar case of periosteal abscess, six months post-typhoid, found this bacillus alone. Achalme[*] cites a case of periosteal abscess of tibia, the pus of which showed only the typhoid bacillus; and Melchior[†] found this organism alone in a periosteal abscess of the tibia occurring ten and a half months after the attack. Golgi and others have had similar expérience. In these cases the bacillus of Eberth was regarded as the sole infective agent.

At about the same time Pean and Cornil[‡] reported a case of necrosis of the tibia, occurring eight months after recovery from typhoid fever, examination of which showed the typhoid bacillus associated with other organisms.

Fashing[||] reported a somewhat similar case, in which staphylococci alone were found.

E. Fraenkel[§] found pyogenic organisms associated with the typhoid bacillus. He does not think that the typhoid bacillus plays an important *rôle*, but holds that the condition is one of secondary infection by the pyogenic cocci, and where these have not been found they have died out or the culture medium has not been suitable.

From time to time a large number of cases have been observed, varying more or less in the character of the infection. Thus Achalme, Melchior (as above stated), Sultan, Chantamesse, Widal, and others have reported cases of pure typhoid infection. Klemm speaks of a mixed infection, with the colon and typhoid bacilli; and one of our own cases showed the typhoid bacillus associated with the staphylococcus pyogenes citreus.

There are many cases on record in which the infection has not been with the typhoid bacillus, but with the pyogenic cocci, or the less frequent pus producers. Netter describes eleven cases of ostitis, five of which showed the pneumococcus, one the pneumococcus and staphylococcus, and five the streptococcus.

While it is certain that mixed infections do occur in these post-typhoid bone lesions, it must be admitted that the evidence of careful bacteriological investigation, based upon a considerable number of cases, is to the effect that these lesions may be caused by the typhoid bacillus alone.

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[*] La Semaine Médicale, 1890, T. X, p. 224.

[†] La Semaine Médicale, 1892, T. XII, p. 304.

[‡] Bull. de l'Académ. de Méd., 1891, No. 15.

[||] Wiener klinische Wochenschrift, 1892, No. 18.

[§] Baumgarten's Jahresbericht, VI, p. 225.

The question of the pyogenic properties of the typhoid bacillus is of great interest in connection with these sequelæ of the fever.

Orloff produced suppuration in dogs and rabbits by subcutaneous inoculation of pure typhoid cultures, the pus showing this organism alone. Adenot,* by similar inoculation, caused pus formation in the subcutaneous tissue of dogs and rabbits; the typhoid bacillus was separated in pure culture.

Of greater interest, in the consideration of bone lesions, are the experiments of Golgi, who fractured a long bone in one of the lower animals, and at some distance from that point injected subcutaneously a suspension of pure typhoid bacilli, with the production of suppuration at the point of fracture; the pus showing in culture only typhoid bacilli.

The presence of the typhoid bacillus in the spleen and bone-marrow, particularly of the ribs, has been demonstrated by Quincke as late as the seventh week of the disease. In nine cases examined eight showed the organism in the marrow of the ribs. In two cases the sternum was examined with positive results, and in seven out of eight cases large numbers were found in the spleen pulp. By analogy they should be as frequent in the bone-marrow as in the spleen. The autopsy records of the Johns Hopkins Hospital show many instances in which typhoid bacilli have been found in the different organs of the body, in the bone-marrow and bile.† Dr. Welch has observed their persistence in the bile of a rabbit which had been inoculated four months previously and had recovered; they were not found in the organs. As showing the tenacity of life of the organism, Schiller implanted the bacilli on a silk thread, and at the end of one year they were found still living. According to the same author they can exist on a potato culture for two years.

Ufflemann, found the bacilli alive in dry sterile sand at the end of eighty-two days.

These points throw some light upon the occurrence of post-typhoid bone lesions at periods long after the primary attack, which, as will be seen later, is one of the striking clinical features. It is moreover, on these grounds that the theory of mixed infection is based,—that the pus cocci upon a soil already vitiated by the presence of the typhoid bacillus determines the suppuration, the pus organisms later dying out and leaving the bacilli alone in the focus, but it is an open question as to whether or not this really does occur. The experiments of Klemm have a very significant bearing upon this point. Into the ear vein of a rabbit he inoculated a pure culture of typhoid bacilli, and seven days later, in the same animals, and in the same manner, inoculated a pure culture of staphylococcus pyogenes aureus, with the result that an osteomyelitis—with, in one case, separation of the epiphysis—was set up, cultures from which showed the staphylococcus pyogenes aureus alone. Again, by the inoculation of both organisms together he produced an osteomyelitis of the ilium, cultures from which also showed staphylococcus pyogenes aureus alone.

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* Archiv. de Méd. expérimentale, T. I.

† Flexner, Journal of Pathology and Bacteriology, April, 1895.

The problem of the etiology of the post-typhoid bone suppurations appears to be twofold. Observations upon suppurative processes in human beings, developed during or subsequent to an attack of typhoid fever, indicate that at one time the ordinary pyogenic organisms are alone present, at another, associated with the typhoid bacillus, and in still others the typhoid bacilli alone are met with, and even more rarely the typhoid bacilli are found together with other bacteria—*e. g.*, bacterium coli commune. It is not necessary that there shall be a common etiology in these processes any more than we look for a common cause of suppurative processes occurring under other conditions in the body; on the other hand, there seems to be no good reason for excluding the typhoid bacillus from the group of possible pyogenic micro-organisms. It may be looked upon as capable of causing various pathological conditions,—a specific typhoid fever attack, a local suppuration, and, finally, a general septicæmia, as in a case which recently occurred in this hospital and was reported by Dr. Flexner.* The pyogenic organisms are often present in the intestine, and it is not surprising that they should also, at times, penetrate the interior when a ready means of entrance is afforded by the open ulcers present.

During the past year six cases of post-typhoid bone necrosis have come under our notice. Four were admitted to Dr. Halsted's service in this hospital, to whom I am indebted for the privilege of reporting them. The other two we were able to study in private practice through the kindness of Dr. Osler and Dr. Finney.

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* Journal of Pathology and Bacteriology, April, 1895.

Case I.—A. T., aged thirty-five years, cigar-box maker, admitted to Ward E, March 19, 1894, with a discharging sinus over left costal margin. The family history was negative. Inquiry into the previous history revealed no serious illness. There was no history of venereal infection. He had typhoid fever in August, 1893, the attack lasting three months. During convalescence, and while still in bed, patient suffered from what he describes as constant sticking pains over left costal margin, more or less severe, to which the attention of the physician in attendance was frequently called.

In November—*i. e.*, one month after recovery from attack, the pains, however, persisting—there appeared an inflammatory area over the left costal margin, high up towards the xiphoid cartilage. There was no cough, no dyspnœa.

In December an incision was made into the tumor, blood escaping (according to the patient's description), after poulticing for some time a purulent discharge appeared which has persisted.

On admission the general condition was good. Examination of the thoracic and abdominal organs was negative. There were no glandular enlargements; the note on condition of chest wall is as follows:

Midway between xiphoid cartilage and the left nipple is a bright-red inflamed area, two by two centimetres, and in the centre of this the opening of a sinus. A probe passes three centimetres into the sinus backward and downward to the cartilage of the seventh rib. Around this inflammatory area the tissues are denser than normal and slightly painful to the extent of ten centimetres from above downward, and eight centimetres laterally. Highest temperature record 99.5° F. Urine was negative; no diazo-reaction.

Operation March 22nd, 1894.—Dr. Bloodgood. The granulation tissue was found behind the seventh costal cartilage, which was perforated. Posterior periosteum was not incised, but curetted. All diseased soft parts removed. The wound was irrigated and loosely closed. The cartilage was perforated in three places from cavity to sinus.

By March 26th some of the stitches were removed. Wound in central part gaping; slight bloody discharge. The wound showed little tendency to granulate.

April 2nd.—Patient was discharged. The sinus was still present, discharging a brownish pus.

April 6th.—Patient returned for dressing. A swelling was noticed over the left costal margin below wound of former operation. Healthy tissue separates the two. There is pain in the swelling and in lower part of back on same side.

April 12th.—Patient readmitted to Hospital. Wound of former operation looking well, granulating from bottom well; sinus still discharging; swelling over costal margin below is as at last note, but more painful. There is no redness, no œdema; severe pain in back and left side low down.

April 15th.—A friction murmur was heard just above the swelling; fluctuation was evident in tumor; pain was not so severe as at time of last note.

April 19th.—Pain in swelling much greater; fluctuation more marked; friction murmur no longer heard.

April 19th.—Operation: Dr. Finney. Excision of old sinus and some cartilages; opening of abscess over costal margin; much thick greenish-yellow pus evacuated; wound irrigated (1 to 1000) hydrarg. bichlor. solution; packed with iodoform gauze. Shortly after operation the patient left the Hospital, returning every few days for dressing.

May 11th.—Wound granulating rapidly; no cartilages exposed.

May 29th.—Wound healed except at two points; all pain has left the back for the last two weeks.

August 1st.—There is a small sinus discharging very little pus in centre of last wound; general health is much improved; the cultures at this time showed the typhoid bacillus and staphylococcus aureus.

December 14th, 1894.—Wound perfectly healed, scar depressed, and it looks healthy; there is no pain; scar runs parallel with left costal margin, five centimetres above it; patient says wound has been completely healed since August 15th; the only symptom is a feeling of numbness along costal margin corresponding to the scar.

Bacteriological Report.—March 22nd, 1894.—Culture at operation, agar slant made; the pus was noted as being thick and gelatinous, and a general necrotic condition existed about the focus; twenty-four hour growth plated.

March 23rd.—Petri plates of yesterday show large and small grayish colonies. Under low power, large colonies, circular and oval, granular generally, with darker circumscribed centres. In the paler periphery darker spots are seen like the centre, but smaller. Cover-slips from both large and small colonies showed short bacilli with rounded ends, growing often in pairs, which stained faintly; also longer bacilli forming long threads.

Agar slant from colony in twenty-four hours shows uniform grayish growth along smear; after several days fringe-like growth from edges; sour smell.

Gelatin rolls: whitish or grayish colonies spread out on surface, and small darker deep colonies. The superficial colonies had dark yellowish centres, the periphery being much paler and of a gray color; the edges were uneven and wavy; no liquefaction of the gelatin.

Low power: in places a double fringe is noted at the edge; the markings in outer part are mostly parallel with border, or nearly so.

Bouillon: clouding in upper zone. Potato: no growth perceptible. Cover-slip showed the same organisms as the above.

Litmus milk showed faint reddening; no coagulation.

Lactose agar, 1 per cent.: no fermentation, though abundant growth along the stab.

Indol reaction: with and without nitrite, negative; parallel culture of colon positive. Hanging drop preparation showed the organisms very motile. The appearance of the cultures remained unchanged after many days. Plated with Hg: marked double zone about Hg.*

About one month after first operation cultures from the sinus showed typhoid bacillus in pure cultures.

Fourteen weeks after second operation cultures from sinus showed typhoid bacillus and staphylococcus pyogenes aureus.

Conclusion: Typhoid bacillus.

Case II.—S. M., female; married; aged forty-three years; admitted to hospital April 2, 1894.

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* Bolton, International Medical Magazine, December, 1894.

There is a definite tuberculous history. Diseases of childhood; scarlet fever; one miscarriage (at second month); pneumonia ten or twelve years ago; patient has expectorated blood several times during last winter, at times bright red, and at times mixed with sputum; two ounces was the largest quantity at any time.

P. I.—Typhoid fever in September, 1892; was up and about in following November.

In January, 1893, she began to have pain in right side over lower ribs, and noticed that the soft parts over painful area were more prominent than on left side. Pain over lower ribs on coughing and on drawing a long breath; this pain over lower ribs became less, but never entirely disappeared. Six weeks ago noticed soreness over seventh, eighth and ninth costal cartilages on right side; a few days later noticed that the skin was purplish in color, and that there was a hard swelling over the seat of pain. This swelling became very painful and gradually larger. Poultices have been applied, and a small projection has formed on its surface.

S. P.—General health good; condition described as above; the swelling was incised in the ward, and cultures were taken; urine negative; no diazo-reaction.

April 6th.—Operation: Dr. Finney. Excision of sinus and costal cartilages of seventh and eighth ribs. The sinus leading downward and outward begins to the right of the ensiform, extending to the cartilage of the seventh rib, which is perforated. Other sinuses were formed behind this, and between it and the sixth, and between it and the eighth. These sinuses were lined by soft reddish granulation tissue; the perichondrium was thickened; cartilages and sinuses were excised; some cartilage was left in the wound; iodoform gauze packing after irrigation with (1 to 1000) hydrarg. bichlor.

April 9th.—Wound granulating, except over cartilages in floor of wound; temperature 104° F.

April 18th.—Granulations healthy, except over exposed cartilage. Temperature 99° F. on April 12, to-day temperature is normal.

May 30th.—Patient was discharged. Sinus still discharging. Patient to return for dressing.

June 13th.—All healed, except over small point of exposed cartilage. Some pain over ribs under angle of scapula.

June 23rd.—Sinus curetted. Bacilli and micrococci found in cover-slips of discharge.

June 26th.—Patient was readmitted for operation.

June 28th.—Operation: Dr. Bloodgood. Three cartilages found involved. They were excised as far as costal junction from sternum, at which points the periosteum was not thickened, and cartilages appeared quite normal. At all other places the periosteum was adherent and thickened, sinuses filled with granulation tissue, and the cartilage was riddled with small sinuses. Highest temperature since discharge was 102° F.

July 3rd.—First dressing; doing well.

December 20th.—All healed except small area, more an excoriation than granulating area; slight dermatitis about it. Breast is pendulous and hangs over wound. There is no sinus. General condition is good. Wound has been healed about two weeks.

Bacteriological Report.—Cover-slips and agar slants were made from pus obtained when mass was first incised.

Cover-slips: bacilli varying in length from two times to several times as long as broad.

Agar slant (forty-eight hours): whitish growth along line of smear and stab; tendency to run out from stab by sort of fringe. Growth plated.

Petri plates: show colonies as in *Case I.* Only one variety of organism—isolated.

Gelatin slant (forty-eight hours): grayish-white raised colonies; glistening surface, outline wavy; centre more opaque than periphery; colonies quite discrete; shapes vary; no liquefaction of gelatin.

Cover-slips show bacilli mostly short with rounded ends; some straight, others slightly curved; also very long bacilli; segments not well marked.

Gelatin rolls (seven days old): grayish-white colonies spreading out on surface; centre more opaque than periphery; edges uneven and wavy.

Low power: central mass brownish and granular; periphery paler, gray; darker markings, mostly linear; margins uneven and wavy; no liquefaction.

Litmus milk: very faint reddening; no coagulation.

Potato: no visible growth (cover-slip showed organisms).

Lactose agar: no fermentation; abundant growth.

Indol reaction: with and without nitrite, negative; parallel cultures of colon, positive.

Motility: actively motile; the field shows short, very motile bacilli; also long threads traversing the field with wavy motion.

Plate with Hg: double ring and sterile zone; zone about seven millimetres wide.

Six weeks after first operation cultures from sinus showed typhoid bacilli and staphylococcus pyogenes aureus. Most of primary tests were repeated for confirmation.

Conclusion: Typhoid bacillus.

Case III.—J. K. (Hos. No. 10,792), male, aged thirty-six years; married: German; tailor; admitted to hospital September 5, 1894, complaining of painful swelling over right tibia, and discharging sinus over left tibial crest.

Family history unimportant.—Previous history: no serious illnesses with exception of typhoid fever in October, 1893. No history of venereal infection. Habits: smokes and drinks moderately. The patient was taken ill with typhoid fever on October 4th, 1893, was in bed four weeks, and for two weeks was very delirious; early in November patient was up and about. During the three weeks after rising from bed the patient experienced vague pains first in right arm and forearm for a few days, then in left leg, then over right costal margin, these were slight and soon passed off.

On November 26th there was more acute pain over *left tibial crest*, increasing in severity, and later redness and swelling. Early in December incision was made into the swelling with instant relief. About the middle of December incision was necessary in another spot above the first, and on February 1st another incision was made below the others, when a splinter of bone was removed. The sinus is still discharging. There was no pain after first operation. Patient was able to work until time of admission to Hospital.

Right Leg.—In November, 1893, a slight pain was noticed in the right leg over tibial crest, and a small hard nodule the size of a small nut was found. The pain was always present, but very slight. There was no history of trauma. This remained so from November, 1893, to September 1st, 1894, when the nodule became red and painful, and on September 5th the patient was admitted to Hospital.

S. P.—General condition good; thoracic and abdominal organs negative; temperature has not been higher than 99.5° F. since admission; urine negative.

Right Tibia.—The middle third is occupied by a fusiform enlargement, twelve centimetres long by five centimetres wide. This area is remarkably reddened and brawny, and the skin is œdematous. Over the most prominent point fluctuation is distinct, the area of fluctuation being definitely outlined. The entire involved area is very tender; there is constant pain, more or less severe.

Left Tibia.—About middle of crest is a small sinus opening, five by five millimetres, surrounded by dense inflammatory tissue. There is slight purulent discharge from sinus; probe passes two centimetres down to bone.

September 6th.—On the day following admission the right leg was prepared as for operation, and with all possible care the fluctuating mass was aspirated for bacteriological purposes; about ten cubic centimetres of a brownish-red fluid was withdrawn; this was of a very gelatinous consistence, and was odorless; this was plated immediately.

September 7th.—The condition of right tibia has almost completely subsided; redness and swelling with pain are much less marked.

Operation: Dr. Werckmeister.—Right tibia shows periosteal abscess containing brownish-red gelatinous exudate. This was completely excised; bone beneath found not involved; wound packed with gauze.

Left Tibia.—On stripping back periosteum from front of tibia, two new bone sinuses are found and the surface of the bone rough; this was chiselled away and further sinuses with soft bone granulations and pus were found. All the anterior part of bone was removed, and back near posterior wall a sequestrum, one centimetre by one millimetre, was found; the operation was very extensive; only the posterior wall of the bone was left; the diseased skin excised. Pure carbolic acid was applied and irrigation $\frac{1}{1000}$ $HgCl_2$; gauze packings were used; secondary sutures were passed.

September 10th.—Left leg doing well; secondary suture tied; right leg also doing well.

September 16th.—Left leg is doing well; slight sero-purulent discharge; general condition good.

Bacteriological Report.—September 6th.—Right tibia. Fluctuating mass aspirated; grayish-brown pus, very gelatinous and sticky, apparently no curds nor shreds in it; it contains some blood.

Petri plates, agar slants, and cover-slips were made at once. Cover-slips negative; although many leucocytes and red blood-corpuscles were present.

Plates (twenty-four hours): Colonies were: superficial (I) and deep (II). Colony I: About five millimetres in diameter, slightly raised, centre small, dense, and white periphery grayish, also rather dense, edge regular, surface glossy.

Cover-slip: Short segmenting bacillus with larger forms; agar slant made; other colonies are paler, but the organisms were apparently similar. Colony II shows same organisms as No. I.

September 8th.—Colony I: Agar slant (twenty-four hours): grayish, pearl-like growth along line of smear; a fringe-like unevenness along edge.

Gelatin stab (six days old): free growth along stab of small white colonies; no liquefaction.

Bouillon (twenty-four hours): slight cloudiness, granular sediment.

Litmus milk (twenty-four hours): faint reddening, no coagulation.

Potato (twenty-four hours): no visible growth.

Lactose agar (twenty-four hours): faint growth along stab; no fermentation.

Hanging-drop preparation showed organisms very motile as short rods; also long chains of larger organisms were seen having a wavy motion across the field.

Indol reacti[illegible] H_2So_4) with and without nitrite, negative.

Culture (ten days old): still no visible growth on potato; no fermentation; no coagulation of milk, only faint pinking; no color to agar cultures.

Conclusion: Typhoid bacillus.

Case IV.—H. H., male, aged twenty-nine years; traveller; admitted to hospital December 1st, 1894, complaining of inflammatory condition over crest of right tibia. Family history negative. Personal history: *Childhood,* measles, mumps. *Adult life,* vague history of malaria. Venereal history: gonorrhœa six years ago, four-and-a-half years, and three years ago; recovery apparently complete. Habits: alcohol in moderation; smokes but does not chew tobacco. Patient was in Ward C from October 8th to November 2nd with typhoid fever; had been ailing about ten days (three days in bed) previous to admission.

Present Illness.—While still in bed during convalescence from typhoid fever there was pain in right foot and discharge of small amount of pus from just below right fifth toe. At the same time there was also considerable pain over right tibial crest, markedly worse from 5 to 12 p. m.

After leaving hospital pain became much less severe, almost unnoticeable. From November 8th to 24th only occasional very slight pain.

From November 24th gradual increase of pain, worse at night; no history of any trauma, but patient had been almost constantly on his feet.

November 26th.—A swelling appeared over crest of right tibia; no reddening of surface. There was increase of pain until November 28th.

November 29th.—Incision was made into the mass; no pus escaped, only blood, giving immediate relief from pain.

Patient was admitted to hospital December 2nd, 1894. General condition good; thoracic and abdominal organs negative. Urine, 1035, acid, sweetish odor. Chemically: phosphates; no albumen; no sugar; no diazo. Microscopically negative. Over right tibial crest is a uniform enlargement seven centimetres from above downward, in the centre of which is an opening three centimetres long, slightly gaping, the seat of former incision. There is no pain, but the part is very tender. There is no rise in temperature. Patient feels well. No bare bone is felt in wound; wound is filled with blood clot.

December 4th, 1894.—Operation: Prof. Halsted. A thin layer of bone was chiselled away. Excision of diseased tissues; wound closed with silver skin stitches after thorough irrigation with hydrarg. bichlor. (1 to 1000).

December 13th.—First dressing; doing well; cultures taken.

December 21st.—Patient was discharged; wound almost healed; slight granulation along incision.

March 17th, 1895.—Wound entirely healed; no pain.

Bacteriological Report.—Operation, December 4th, 1894. The pus was of grayish-yellow color, thick, but not tenacious; no odor. Granulations necrotic, surrounding tissues, especially muscle, markedly necrotic, and of translucent, hyaline appearance. Bouillon and agar slant cultures made at time of operation; also cover-slips of pus.

Cover-slips negative as regards organisms.

Three hours after the first cultures were taken Petri plates made from bouillon cultures and from pus that had been put on the agar slant.

December 7th, 1894.—Agar slants and plates, discrete grayish colonies, irregular outline, pearly lustre, slightly raised.

Cover-slips: short, moderately thick bacillus; length, two or three times the breadth; ends rounded. Also larger forms in shape of longer and somewhat thicker bacilli; no threads were seen. Agar slant made from a discrete colony. Agar slant (forty-eight hours) shows pearly growth along smear.

Gelatin stab (three days): free growth along stab; no liquefaction.

Inoculations upon potato (twenty-four hours) showed no visible growth. (Organisms in cover-slips.) Litmus milk (twenty-four hours): very faint pinking, no coagulation. Dunham's solution (twenty-four hours): clouding. Glucose agar (1 per cent., twenty-four hours): distinct growth along stab; no fermentation. The organism is very motile; in the field it is seen as short, single bacilli (very motile), and larger, longer forms (less motile).

Indol reaction (the culture having been in Dunham's solution), with and without nitrite, proved negative. Petri plate with Hg gives wide sterile zone and a double fine ring.

January 4th, 1895.—The appearance of the cultures of December 9th, 1894, is still unchanged.

Conclusion: Typhoid bacillus.

Tissues removed at operation: Dr. Bloodgood. The sinus over the tibia is 3.5 centimetres; seven millimetres removed with a margin of skin from .5 to 1 centimetre wide. The sinus leads to a cavity at the bottom of which is the thickened periosteum, beneath which there has been a formation of new periosteal bone, easily stripped from the surface of the old shaft in thin laminæ. The bone itself shows no marked pathological changes. The periosteum is thickened from three to four millimetres, is grayish in color, and opaque. The granulation tissue of the cavity is grayish and glistening, dotted with fine pin-point red spots, and does not differ from that seen in a syphilitic periostitis, but the tissue about this cavity shows marked changes not noted in syphilitic periostitis.

The aponeurosis of the muscle is thickened and more opaque in color. The muscle has lost its bright red color and is gray. One sees in this tissue beneath the skin and parallel to it alternate white and red streaks.

Case V.—Miss T., aged twenty-one years, was brought to Dr. Osler, on November 23rd, 1894, by Dr. Bishop, complaining of general debility and a sore leg. I am indebted to Dr. Osler for the notes of the case.

She has never been a strong girl, had always had poor digestion, and throughout the summer of this year was not at all well. In August she had an attack of fever, which began with headache and vomiting. She was extremely weak, and Dr. Bishop suspected typhoid fever. After persisting for a couple of weeks the fever subsided, but in ten days there was a slight return. The doctor remained uncertain about its nature, as she never had diarrhœa or any abdominal symptoms. Early in October she began to have great pain about the middle of the right tibia, and also on the front of the left forearm. Swelling soon followed in both regions, and on the leg a phlegmon developed, with much redness and swelling. This was lanced about a week ago by Dr. Bishop, and discharged a quantity of pus. The inflammation at the middle of the right arm gradually subsided.

Present Condition.—She is healthy looking, complexion not very good, owing to the presence of numerous pimples. The tongue is a little furred. The pulse is good, and there is no fever. The right leg is very much swollen from the ankle to the knee. In the middle of the anterior surface there is a large area of redness over which the skin is glossy, and an incision about two centimetres in length, from which a thin, sanious pus exudes. There is pitting above the ankle and a good deal of tenderness in the leg, but she is able to walk upon it.

On the left arm about the middle of the shaft of the radius there is a swelling about three by two centimetres, which projects quite prominently. The skin is not reddened and not adherent. It feels firm and is very sensitive to the touch. The patient was transferred to the care of Dr. Finney.

November 30th, 1894.—Operation: Dr. Finney. Left radius. Over lower end on ulnar side was a slight elevation, very painful; no redness over surface. Incision in long axis of arm, four centimetres in length, down to periosteum of radius, which was found thickened and adherent to bone beneath. This was turned back and exposed a bone of spongy consistence. This was incised; and pus of a grayish color and thick consistence was found and removed. A distinct cavity was found in the bone, containing a small sequestrum ten by two millimetres. The cavity was curetted and iodoform gauze packing inserted. The skin wound was partially closed about the packing. Cultures were taken; much pus was placed upon an agar slant.

Right tibia.—Over crest of tibia about the middle was an incision wound about three centimetres long, discharging a brownish pus, seat of former operation. Above this the skin is much discolored and of purplish color and very thin; there is distinct fluctuation.

November 30th, 1894.—Operation: Dr. Finney. The old wound was excised, and the incision was extended up through fluctuating point above; a dark, brownish-colored pus of viscid consistence was evacuated. The skin was much undermined, and a regular phlegmonous condition existed. Cavity and pockets were well curetted and packed with iodoform gauze, after irrigation with hydrarg. bichlor. solution (1 to 1000).

Bacteriological Report.—Left Radius: Osteomyelitis; with sequestrum formation.

Right tibia.—Periostitis with phlegmon above seat of lesion subcutaneously.

November 30th, 1894.—Petri plates and slants were made from the pus twenty hours after operation. Cover-slips made from the pus were negative.

The original agar slants show discrete colonies after twenty-four hours. From radius colony I shows colonies of irregular outline, grayish, pearly surface, slightly raised. With transmitted light there is a distinct pearly lustre; the centre is more opaque and more yellowish than the periphery. Cover-slips show short, thick bacilli with rounded ends, also larger forms. Colony II is round, with regular outline, raised surface shiny; the difference between centre and periphery is not very marked, the latter being slightly paler and thinner. Cover-slip shows a coccus,—singly, in pairs, and in groups.

Colony I.—Agar slant (five days old): uniform grayish film over surface (the agar is very moist). Cover-slip as above.

Gelatin stab (two days): distinct growth; no liquefaction. Potato (four days): no visible growth; organism on cover-slip. Litmus milk (four days): faint pinking; no coagulation.

Organism was found very motile. Dunham's solution (two days): faint clouding. Indol reaction, with and without nitrite, negative.

Glucose agar (two days): Distinct growth along stab; no fermentation.

In some cases there was a yellowish filmy growth on potato, likely due to some peculiarity in the medium, as other cultures gave an invisible growth.

All these cultural tests were repeated later, giving the same results as above, excluding the visible growth upon potato.

Colony II.—Agar slant (five days): general growth of small pin-head colonies, now assuming a yellowish color.

Gelatin (several days): distinct growth along stab; liquefaction of nearly half the gelatin. Potato (seven days): distinct lemon-yellow growth. Litmus milk: faint pinking; no coagulation; no further change at end of six weeks.

Dunham's solution (seven days): slight clouding.

Glucose agar (seven days): distinct growth; no fermentation.

Right tibia: the pus was of brownish-red color, was odorless, thick and gelatinous.

After five days the original agar slant showed discreet colonies, whitish or yellowish in color, having circular, regular outlines; surface being raised.

The cover-slip showed a small coccus, in pairs, groups, and chains of four to eight.

Agar slant (two days): shiny, pearly growth, regular margins, slightly raised.

Gelatin stab (two days): growth along stab; slight liquefaction. Potato (one day): dry, raised, golden-yellow growth. Litmus milk (one day): no change as yet. Dunham's solution (one day): slight clouding. Glucose agar: yellowish growth along stab; no fermentation.

Twenty days later. Potato: rich golden-red growth, raised and dry. Litmus milk: decided reddening; no coagulation. Gelatin: marked liquefaction.

At the end of seven weeks. Potato: as above. Litmus milk: a solid yellow coagulum. Gelatin stab: four-fifths of medium liquefied.

Conclusion: Staphylococcus pyogenes aureus in the right tibia; in the left radius the bacillus typhoideus and the staphylococcus pyogenes citreus.

Case VI.—In the practice of Dr. Osler. Dr. —— had typhoid fever from March 8 to April 25, 1894. During the past two months he has been at work. While still in bed he noticed a twinge of pain just above the left costal margin; it has increased and extended along the eighth rib; there is now on this rib, from mid-axilla to nipple line following the course of the rib, a definite swelling, which causes slight projection of the skin, which, however, is freely movable and uninvolved; there is no fluctuation, no special soreness, except on deep pressure.

His general condition is excellent; he looks well; tongue is clean; percussion is clear over the axillary and lower mammary regions; no pleural friction; a few small crackling, probably pleural râles on deep inspiration over mass.

It is so firm and hard, and his general condition so good, that he will wait a month to see if it will not resolve spontaneously.

Though the doctor looks well and strong, and has gained in weight and strength, he has still a little fever every day.

The case was seen on June 30, 1894; guaiacol was used locally three times a day until September 1st, when patient thought he was all right; during September and October patient was well; no pain; no enlargement noticeable.

All went well until the middle of November, when the place became a little tender again; there has been gradual enlargement with pain since; the swelling is now two-thirds as large as it was in June last; the temperature shows ½° to 1½° F. elevation each day.

This was by note to Dr. Osler, December 14, 1894. The last report from the patient was in June, 1895, when he states that the swelling has again subsided, leaving only a painless induration in its place.

Of six cases four occurred in men and two in women. In the reported cases the condition has been more frequent in men.

The ages ranged from twenty-one to forty-three years. Age is not believed to be a factor of any importance.

In a majority of cases the character of the typhoid fever attacks bears no relation to the occurrence of these lesions. It was very difficult to obain any correct account of the attack in most of these six cases.

The period after recovery from typhoid fever at which the lesions appeared varied from one to sixteen months. In two it was one month, in one two months, in another ten months, in another sixteen months, while in the remaining case the condition has not yet gone on to necrosis, but has recurred and subsided spontaneously now for the second time.

Sir James Paget described this condition as coming on when the patient was "well of his fever" when the temperature had already become normal, and convalescence was well established. I have been unable to find, with one exception, that of Ebermaier * an authentic case appearing during the course of the fever, though several have followed very early in convalescence. A large number of instances, however, of suppuration in the soft parts, either of typhoid or mixed infection, are on record, but the above case of Ebermaier's was a pure typhoid infection occurring on the thirteenth day of the fever. The latest instances range from between ten and a half and eighteen months after the subsidence of the fever.

As to the bone involved, hardly any region of the body is exempt. The tibia is undoubtedly the bone of choice, instances in this situation greatly predominating. The humerus, radius, ulna, femur and fibula have at one time or another been involved, whereas the feet and hands are remarkably free, a case observed by Ebermaier being the only instance I can find. In the head, the parietal and temporal bones have

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* Deutsches Archiv für klinische Medicin, 44, 1888–89, p. 141.

been affected, and in the thorax the ribs or their costal cartilages are a very common seat, probably next in frequency to the tibia. The so-called typhoid spine, supposed to be an example of the same condition in the vertebral column, is probably a neurosis. As stated above, the rarity of cases in which the hands or feet were involved is quite striking. In this connection I might say that recently a patient came to the out-door clinic of this hospital, and in giving his history spoke of an attack of typhoid fever some eight or ten years previously. On his right hand a cicatrix was noticed on the dorsal surface between the third and fourth knuckles, and on being questioned regarding it, he gave the history of an inflammatory swelling which came on during convalescence from typhoid fever (two weeks after the fever had subsided), broke down, was opened, and healed after nine weeks' treatment. Possibly this is a case in point.

In the cases here reported the lesions were in three cases in the ribs or their costal cartilages, in one case in the tibia, in one both tibiæ (only one being worked out bacteriologically), and in one the left radius and right tibia.

Usually the first symptom is pain. In three of our cases this was complained of while the patient was still in bed convalescing from his typhoid fever, in the others soon after being up and about. The pain is usually localized, but in one of these cases was widely disseminated, shifting from one region to another. It almost invariably attacks the region subsequently the seat of the necrosis. The condition has been likened to the bone pains of secondary lues. This pain usually subsides after a short time, becoming almost unappreciable, or leaving but a slight soreness over its former seat. In the painful area a slight swelling may occur, also subsiding with the pain. The duration of the swelling varies; in some cases the trouble soon recurs with pain, swelling, and indications of necrosis; in others this may be delayed for months; while again in others there may be repeated exacerbations and subsidences, never going on to necrosis.

There is, as a rule, an entire absence of fever, and the clinical course is marked by a peculiar chronicity. The symptoms at the time of necrosis are all increased; the pain becomes more severe, the surface temperature is elevated, but there are no constitutional signs. On incision the pain is relieved, but a sinus may continue to discharge for months or years.

Chantamesse and Widal speak of a case of periostitis of the tibia appearing during convalescence, which was treated by incision, the wound remaining open, and still discharging at the time of their reporting the case four years later. Sultan has observed a case of necrosis of the ribs discharging spontaneously, and persisting with sinus formation for six years.

Cases II and *III* are instances of what has been previously described by Chantamesse and Widal.* In both the initial pain appeared shortly after recovery from typhoid fever, while the patient was up and about. This pain was accompanied by some thickening of the tissues in the painful part. Within a short time both pain and induration subsided, but not entirely, and there remained in *Case II* a noticeable induration with more or less tenderness, but no actual pain; while in *Case III* a definite rounded periosteal node persisted causing no inconvenience whatever. This condition lasted for fourteen and ten months respectively, at which times, from no apparent cause, a sudden exacerbation took place, both rapidly going on to necrosis. Chantamesse and Widal speak of the condition appearing as a periosteal node or exostosis, or later as a periosteal abscess, which is precisely what occurred in *Case III.* These writers definitely separate these specific typhoid bone lesions from those due to mixed or pyogenic infection. They draw attention to the late period at which the onset follows the typhoid fever attack, to the subnormal temperature, and to the absence of septic signs, and refer to them as "suppurations frôides," likening them to the exostoses of syphilis and the cold suppurations of tuberculosis.

There is a certain proportion of cases in which necrosis does not take place. These of course cannot be subjected to bacteriological study, but they are in every other particular so similar to the foregoing that they may be placed in the same category. Sir James Paget refers to one patient who remained subject to repeated attacks of pain and swelling of the periosteum three years, yet without any sign of suppuration or abiding change of structure beyond a slight thickening. Orloff has observed the same tendency of some cases to resolve. In one series of experimental inoculations † with typhoid bacilli, in a few instances resolution of a definite tumor was noticed, after having existed for quite long periods of time, whereas in others the tumor broke down.

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* Bull. et Mém. Soc. Méd. des Hôp. de Paris, November, 1893.

† Dmochowski und Janowski, Centralb. für Bacteriologie und Parasitenkunde, Bd. XV, No. 7, 1894.

Case VI is an instance in which the node resolved. The onset was, as in the other cases, during convalescence; later the tumor formed over the costal margin, but slowly subsided. Almost eight months 'post-typhoid' it again appeared, and recently—about one year from the onset—the patient reports a second subsidence of the condition, with a painless induration remaining in the affected area.

It may be that some of the cases of "typhoid spine" described by Gibney * should be placed in this class. It has been considered to be a perispondylitis involving the periosteum and fibrous structures about the spinal segments. In many respects its clinical history and course are similar to that of the cases under consideration, except that the pain is so much greater, but here, as in the resolving cases elsewhere, the bacteriological proof is also wanting.

A satisfactory explanation of the occurrence of bone lesions after typhoid fever has not as yet been advanced, but many valuable observations have been made.

The discovery by Quincke of the typhoid bacillus persisting in the bone-marrow after the attack presupposes a lowered vitality and susceptibility of thè tissues so involved, but the setting up of a necrosis in one case and not in another is the point difficult to explain.

As to the influence of trauma, allowing the presence of the typhoid bacillus in the bone-marrow and the resulting lowered vitality, trauma is doubtless in many cases an important factor. There are, however, many instances in which no such history can be obtained, and there are those showing multiple lesions, as that reported by Fürbringer, which can hardly come under this heading.

The effect of overstrain and muscular exertion, as brought out by Keen, is suggestive. He reports the case of a man who some months after recovery from typhoid fever returned to his occupation as rivetter in an iron works, which necessitated much standing and hammering, the strain thus falling mostly upon the right arm and leg. There shortly appeared a swelling of the right arm, and later formation of fistulous tracts through which pieces of dead bone came away.

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* Transactions of American Orthopædic Association, September, 1889, and Johns Hopkins Hospital Reports, Vol. IV.

After recovery he returned to work, whence a similar condition appeared in the right thigh and later in the left. The interesting point is that the lesion of the arm was at or about the deltoid insertion, and that of the right thigh at the insertion of the glutæus maximus, and that of the left at the lesser trochanter, all these being points upon which strain would fall in such acts as standing and hammering.

In the cases of typhoid spine reported by Gibney, a definite history of injury was given in two, but in many others no such history can be obtained. Of the fourteen cases reported by Chantamesse and Widal, three showed a predisposing cause in an old fracture callus. *Case IV* was treated in Ward C of this Hospital during the attack, and while lying quietly in bed he experienced the first pains in the tibia. Subsequently he walked excessively which may have favored the development of necrosis, but he had made no exertion, nor had there been a trauma before the first appearance of pain.

From the bacteriological notes of the cases here reported it will be seen that in four out of the five the typhoid bacillus was obtained in pure culture. The remaining case being a mixed infection, the lesion of the radius showed typhoid bacillus associated with the staphylococcus pyogenes citreus, and the tibia, the staphylococcus pyogenes aureus alone. The wound of the tibia in this case had been opened, and therefore exposed to contamination from without for about ten days previous to the time of taking cultures, but this would not, so far as we know, have resulted in causing the disappearance of the typhoid bacillus had it ever been present. The length of time that these sinuses may remain open and exposed to external contamination and yet be proof against it is very remarkable. In *Case I*, at time of admission, the sinus had been discharging for three months, yet cultures from it showed the typhoid organisms alone. In *Case IV* the exposure was but for a few days, yet it was free from contamination. The most striking example of this, however, is the case reported by Sultan, in which the wound remained open for six years, yet at the end of that time cultures from the open sinus showed the typhoid bacillus unassociated with any other organism. Others have noticed the persistence of the typhoid bacillus in the wound alone, or associated with other organisms, in a large number of instances. Chantamesse and Widal observed one case of six months, and another of four years duration, and D. Buschke has reported a case of abscess of a rib showing the organisms seven years after the attack.

Cases I, II, III and *IV* all showed typhoid bacillus in large numbers before operation. In *Cases I* and *II*, the lesion being situated in the chest wall, and infiltrating deeply into it, all the diseased tissues could not be removed. After the operation the organisms were still found in the wound, which showed little tendency to heal beyond a certain point. Extensive secondary operations were accordingly performed, and yet cultures three and a half months later showed the organism in one of the cases. The necrosis again had deeply infiltrated the thoracic wall. Recovery in these cases was slow.

In *Cases III* and *IV* the lesion was situated in the tibia, and in each case an extensive operation was performed, removing all diseased and suspected tissues, both in bone and soft parts. In *Case IV* cultures were taken at the first dressing on the ninth day, which proved to be negative. In both of these cases recovery was rapid and uninterrupted, the patients being discharged from Hospital—wounds healed—on the twenty-seventh and twenty-first days respectively.

There can be little doubt that the chronicity of the process, and the long periods that the sinuses continue to discharge, are due to the persistence of the organism in the focus. The study of these four cases, though a small number, suggests this very strongly, and points to the fact that complete removal of the diseased tissues alone may be followed by rapid and satisfactory results.

The bacteriological technique in the working out of these cases was as uniform as possible. In three of the five cases the pus was plated in agar almost immediately, and in the other cases the agar slants taken at the time of operation showed the separate colonies so discreetly that they served the same purpose.

In all cases cover-slips from the pus were examined, but in one case only were the organisms found. This difficulty of staining typhoid bacilli in cover-slip appears to have been the experience of many, the explanation lying in the fact that in the first place they stain very poorly, and in the second, that they very readily part with that stain when subjected to decolorizing agents.

The growth on nutrient agar-agar and gelatin, potato, and sugar agar, in bouillon, and litmus milk, and the reaction when subjected to the test for indol, were all characteristic of the typhoid bacillus.

In *Case V*, in some instances a growth was seen upon potato, but subsequent implantations resulted in the usual invisible multiplication of the organism as proved by cover-slip preparations. This visible growth has frequently been met with, but does not disprove the identity of the bacillus as it is considered to arise from some peculiarity in the culture medium.

The test with metallic mercury, as described by Dr. Bolton,* showed the double zone characteristic of the typhoid organism in all the instances in which it was applied.

Morphologically the organism was a short bacillus with rounded ends, freely segmenting, and forming at times long chains. In addition were larger bacilli with ends more square, seen singly, in pairs, and forming long threads. These latter forms were very constant. Nothing resembling spores was seen.

Motility was marked, especially in the smaller forms; in the larger less so. The long threads moved by slow wavy motion across the field of the microscope.

As to the staphylococcus pyogenes citreus and aureus, conclusive descriptions of the cultural reactions obtained are given with the cases in which these organisms occurred.

In the study of these cases the bacteriological considerations are of course the more important, and the pathological considerations are usually dismissed with a few words. The character of the lesion has, however, of late given rise to much speculation with some who would seek to prove it a necrosis rather than a true abscess formation. This has been based largely upon the appearance of the pus, and the microscopical examination of the same. In an article Klemm † speaks of this, and definitely states that a difference exists between the lesion produced by the local typhoid infection and that of the pyogenic cocci. The exudate in the typhoid infections he describes as rich in detritus and containing but a comparatively small number of leucocytes, and he states that it should not be called pus.

The chronicity of the process, so frequently seen, has caused it to be considered by some as analogous to the cold suppurations of tuberculosis, and the necrosis of syphilis, in fact it has been classed with the infectious granulomata. So far, however, nothing has been found in the diseased tissues which can be considered characteristic of, or peculiar to this condition. A small cell infiltration with a greater or less leucocytic infiltration has been seen in all, the development of new tissue varying with the length of time the disease has existed. In some of the more acute, the infiltration is intense, and in one case we have observed a rather diffuse necrosis, as we thought from the gross appearances, but in microscopic examination it was found that nuclear staining was still present, though very faint. In this case (No. IV) the appearances at the time of operation were quite striking. The case was the most acute that we have seen, and came on at the shortest period after the primary disease, and was operated upon six days after necrosis was established. The focus of necrosis was quite circumscribed over the crest of the tibia, but the tissues surrounding it were of a grayish translucent appearance, strongly suggested a condition of necrosis. This, however, as before mentioned, showed faint nuclear staining.

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* International Medical Magazine, December, 1894.

† Archiv für klinische Chirurgie, Bd. XLVII.

As to the pus obtained from these cases, it is difficult to say that there was any characteristic feature. In *Cases I* and *III* the pus was of a brownish-red color, very thick and gelatinous and odorless. In *Case IV* it was grayish in color, thick, but not tenacious, and also odorless. Whereas in *Case V* (tibia), which showed the staphylococcus aureus alone, the pus was apparently identical with that of *I* and *III*, which were purely typhoid cases, in that it was of the same color and equally thick and gelatinous. Examination of the pus showed rods in *Case II* alone. In two of the cases there appeared to be an abundance of detritus present and a noticeably small number of pus cells, many of which showed considerable fragmentation. The gross appearance of all the cases was decidedly ragged and necrotic, though the same must also be said of the tibia in *Case V*, which was a purely aureus infection.

The *diagnosis* of these cases would rest largely upon the history of a previous typhoid fever, or perhaps some indefinite continuous fever. In *Case V* the diagnosis of typhoid fever was made only by the examination of the pus from the radius some weeks after the febrile attack had subsided. The occurrence during or after convalescence is suggestive of the purely typhoid cases, particularly in bone, whereas the mixed infections in bone and soft parts, and the typhoid infections in the soft parts are seen more frequently during the course of the disease.

The *prognosis* is good, as a rule, although in the article just referred to, Klemm reports a fatal case of disease of the femur showing typhoid and colon bacilli associated.

Complete excision of all diseased and suspected tissues appears to be the most satisfactory treatment. In the earlier writings this point was brought out, and mere incision was denounced as being insufficient. The persistence of the organism in the wound for such long periods of time, as some cases show, and the satisfactory results obtained after thorough and complete removal of the focus, suggest very strongly the lines along which to work.

IX.—CHILLS IN TYPHOID FEVER.

BY WILLIAM OSLER, M. D.

In the systematic writers on typhoid fever scarcely a reference is found to chills, except as a symptom of the onset of the disease. Now and again in the journals a case is reported in which chills have been a special feature, and the complication is spoken of as a manifestation of ague. (Short, *Lancet*, 1891, I.) An important contribution to the subject was made at the Association of American Physicians, in 1894 (*Transactions*, Vol. IX), in the discussion which followed the reading of Gilman Thompson's paper upon the concurrence of malaria and typhoid fever. Peabody stated that he had twice seen chills in connection with pyæmic abscesses in the kidneys. He had also seen "severe chills followed by elevation of temperature as a symptom of typhoid fever, which did not affect the subsequent course of the disease; the patient getting well without the administration of quinine, and getting well apparently as other patients do who have not these symptoms." Janeway remarked that the chills were not necessarily due to the development of an intercurrent disease. He held that they were often caused by treatment. "If we give the modern antipyretics in large doses chills will occur, which are due simply to the fact that the temperature has been depressed, and then it rises and this rise is accompanied by mild and sometimes by severe chills. Drop your antipyretics and the chills disappear."

Bouveret,* who has reported four interesting cases, regards the chills as due to an irregular or disturbed elimination of the poison, a large volume of which, thrown into the blood in a short period, may cause a rigor.

(*a*). *At the Onset of the Disease.*

Of 79 cases treated to conclusion during the sixth year of the Hospital work there were thirteen in which the disease began with shaking chills. In two cases there were several severe rigors, in three cases there were two, while in eight the rigor was single.

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* Lyon Médical, 1892.

(*b*). *At the Onset of the Relapse.* (Chart I.)

CASE I.—*Severe primary attack; no chill at onset; normal temperature on the forty-first day; apyrexia for twenty-three days; severe chills at onset of relapse; fever for forty-two days; apyrexia for forty-two days; second relapse, without chills, of fourteen days duration.* (Chart I.)

Tertia C. W., aged 22 (?) (Hos. No. 8488) admitted October 24th, 1893, on the seventh day of the fever. There were no chills at the onset. The fever was high 103°–105.5°, and she had seventy-five baths. The temperature fell to normal on the forty-first day. For twenty-three days there was no fever. On December 20th the fever of the first relapse began, and rose to 103.5° by 10 a. m. of the 21st, when she had the first chill, not a severe one. At 2 p. m. there was a second chill, in which the temperature rose to 106°. A third one occurred on the morning of the 23d, and at 11 a. m. the temperature was 106°. By sponging it was reduced to normal. On the 24th at 3.30 a. m. she had a fourth chill, in which the temperature rose to 104°. The three last chills were severe and she sweated profusely after them. On the 25th there was no chill; on the 26th there was a slight chill at 2 p. m. These five chills initiated a relapse of great severity, which persisted for forty-two days. There was then a period of apyrexia of six weeks, which was followed by a second relapse of two weeks duration. There was nothing in the mode of onset of the first relapse to account for the development of the chills.

CASE II.—*Severe primary attack; severe single chill at onset of relapse.*

Edith T., aged 13, (Hos. No. 6487), admitted December 24th, about the end of the second week of a very severe attack. On January 2nd the temperature for the first time reached normal, and remained throughout the day between 98° and 99°. On January 3rd she had a severe chill in which the fever rose to 105° and fell in the evening to 99°. Throughout the 4th the fever ranged between 104° and 105°. On the 5th it fell to 102°, and on the 6th the

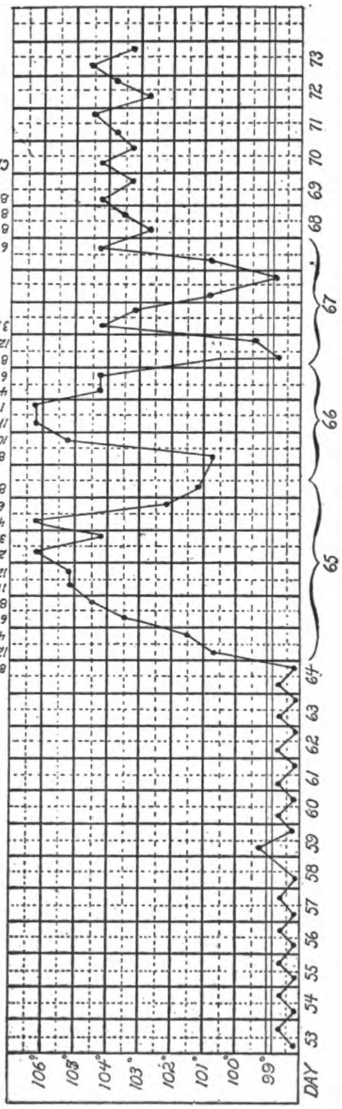

CHART I.—*Chills at Onset of Relapse.*

temperature was normal. After three or four days of irregular fever, there was continuous high fever from the 11th to the 18th, with rose-spots and enlarged spleen.

(c). *Chills as a Result of Treatment.*

Perhaps the most common cause of chills in typhoid fever is the use of medicine, particularly antipyretics. Following a dose of 5 or 10 grains of antipyrin a chill is not infrequent. Last year I saw in consultation a patient who had had chills for ten days and had become very anæmic. The physician thought the chills were septic, and was surprised when I suggested that the antipyrin, which had been given in full doses, was the cause. The chills ceased with the last dose of the medicine.

In one of the following cases a chill followed the injection of a sterilized culture of typhoid bacilli, in two the external application of guiacol.

Case III.—*Chill following a hypodermic injection of sterilized culture of typhoid bacilli.*

Bettie G., aged 27, (Hos. No. 8616), admitted November 12th, 1893. The attack was of moderate severity. On November 15th, 17th and 19th, there were given injections of sterilized cultures of typhoid bacilli. The temperature rose only one or two degrees without rigor or sweating. On the 20th, at noon, when the temperature was 102°, she was given another injection. The temperature rose gradually, and at 1.40 p. m. she had a chill, in which the temperature was 105.8°. It was quickly reduced by sponging. Another injection on the 23rd was not followed by a chill.

Case IV.—*Chill following the application of guiacol to the skin.*

Evelyn H., aged 24, (Hos. No. 9075), admitted January 24th, 1894. The temperature ranged about 104°, and was very little influenced by the baths. For the first week in hospital she was much nauseated, and vomited nearly everything that was given. On the 29th at 4 p. m. guiacol was painted on the skin, as an antipyretic, and again on the 31st and February 1st. After one application she had a slight chill, and on February 1st ♏ xxx of guiacol were painted on the skin of the abdomen at 11.40 p. m. The temperature was 102.2°. At 2 a. m. it had fallen to normal. From 3 to 3.30 a. m. she had a heavy chill, followed by a profuse sweat. The temperature rose very slowly and by 6 a. m. was 102°.

CASE V.—*Chill following the external use of guiacol.*

Elizabeth M., aged 19, (Hos. No. 9158), admitted February 5th, 1894. For the first three days the fever ranged from 102° to 104°. On the 6th, at 8.30 p. m., the temperature was 103.5°; ʒi of guaicol was painted on skin of abdomen. By midnight the temperature was 97.5° and she had a severe chill, after which the fever rose rapidly, and by 2 a. m. reached 104.2°.

(*d.*) *Chills with the Onset of Complications.*

During the height of the fever, or after convalescence has begun, a rigor may precede the development of pneumonia, pleurisy, acute otitis, suppuration in the mesenteric veins, pyæmic abscesses of the kidneys, perforation of ileum or appendix, or an acute periostitis. It sometimes occurs with thrombosis of the femoral or saphenous veins. In rare cases it may precede the development of acute and fatal hyperpyrexia. On the whole, however, rigors are rare in the complications of typhoid fever, as will be noticed in the full analysis which I have given of our cases.

In thrombosis a chill may occur at the onset or recurring rigors may be associated later with suppuration in the clot and with the development of pyæmia.

CASE VI.—*Severe chill with onset of thrombosis of internal saphenous vein.* (Chart II.)

Theodore B., aged 24 (Hos. No. 10298), admitted July 5th, 1894, about the 15th day of the fever. The temperature range was from 103°–104°, and from the 13th to the 15th was almost normal. On the 16th thrombosis of the right internal saphenous vein occurred, with moderate pain in the thigh, but no swelling. The temperature rose, without a chill, to 103°, persisted throughout the 16th, and did not fall to 100° until the morning of the 18th. Then it remained between 99° and 100° until the morning of the 22nd, when, at 6.45

a. m., he had a severe chill, and by 8 a. m. the temperature was 105.5°. The paroxysm lasted for 24 hours, and was followed by heavy sweats. From 8 a. m. on the 23rd the temperature remained normal until the evening of the 26th, when there was a rise to 104.2° without a chill. From this time there was no further fever. There was a marked leucocytosis at the time of development of the thrombus in the left saphenous 21,250 per cm. Four days later the leucocytes had fallen to 5,750 per cm. Subsequently the leucocytes rose during convalescence to above 10,000 per cm., and the patient became a little anæmic.

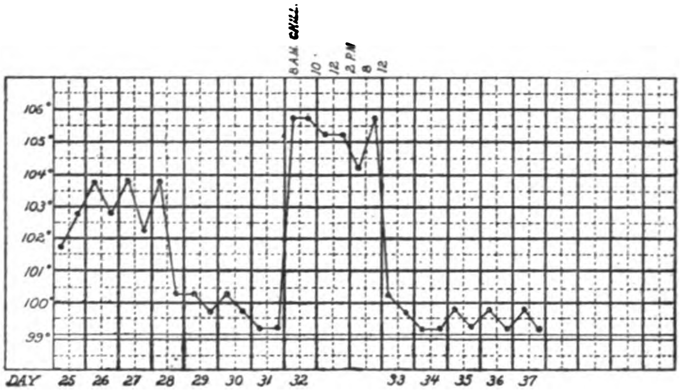

Chart II.—*Chill at Onset of Thrombosis.*

Case VII.—*Severe attack of fever; thrombosis of the femoral vein; eight days later a severe rigor.*

September 23rd, 1895.—While making rounds in Ward F, my attention was called to the patient in Bed 18, whom we found in a severe rigor. He had been very ill for ten days. On the 15th of September a thrombus had developed in the left femoral vein, and the foot and leg were swollen. He had a very dry tongue and was delirious. This morning at 8 a. m. the temperature was 102°. At ten o'clock the chill began, and he shook for twenty-five minutes. The temperature rose during the paroxysm to 105°. He was very cold and blue during the chill, but half an hour later, when I left the ward, he was feeling very comfortable. No further chills occurred.

He became very emaciated, but the temperature fell to normal on September 30th.

In the following case the chill preceded a rapid and fatal rise in the fever:

CASE VIII.—*Admission in the third week, much bronchitis, suffusion of the face, delirium; a severe rigor followed by cyanosis, hyperpyrexia and death.*

While revising this paper, September 21st, 1895, Dr. Parsons came in to tell me that a private patient in Ward C had died suddenly, in a state of hyperpyrexia, after a severe rigor.

The patient, W. W., aged 40, was admitted September 14th. About August 15th, at Ocean City, he first began to feel wretched and miserable. Thinking that the sea did not agree with him, he went to Blue Ridge Summit. About September 1st he became very much worse. The gastric symptoms were very aggravated, and he vomited almost everything he took. He had been treated for malaria. He had had headache and a good deal of prostration, and has taken very large doses of quinine. The temperature at first was moderate, not reaching 104°. He took the baths very badly, was very livid and blue after them, and on September 19th, there was so much bronchitis that it was thought better to substitute the sponges. His pulse was good and the heart sounds clear; but he had constantly a suffused, somewhat ashy appearance of the face. The abdomen was distended and soft. There were no characteristic rose-spots; a few pigmented spots looking like faded roseola. His mental condition was not satisfactory. He was excessively frightened about himself, and on September 17th and 18th tried to get out of bed.

On September 20th and 21st he seemed somewhat better. The temperature had not been high, the morning and evening record for forty-eight hours not above 103.5°. There was a slight trace of albumin in the urine, and a few granular and hyaline casts. A musty, very characteristic odor was exhaled from the skin. I saw him at half-past eleven on September 21st. The bronchitis was better, and I ordered the baths to be resumed. The morning temperature was 102.5°; at 10 a. m. it had risen to 104.3°. At the visit he was sweating profusely, but he seemed better and was rational.

He had taken his nourishment very well. At one o'clock he had a very severe chill, shaking violently. The respirations were hurried, with loud expiratory blowing. The expression of the face was that of fright, and he constantly talked of someone trying to kill him, and called out for help. The pupils were widely dilated and equal; he sweated profusely. At noon the temperature was 104.2°; at 1.45 p.m. it had risen to 106.2°. At this time the chill had almost disappeared. He had become, however, quite cyanosed, the hands purple, the lips blue and the face very dusky; the pulse could scarcely be felt. There was from this time slight twitching of the left side of the face, but no regular convulsion. The cyanosis became more marked, and he became progressively weaker. The temperature rose to 107.5° at 2 p. m., the highest recorded temperature in any case in typhoid fever treated in the Hospital. He died at 2.45 p. m.

(*e*). *Chills (septic ?) during convalescence in severe and protracted cases.*

In a few instances rigors occur throughout the course of the fever, without any local symptoms to account for them. The following cases are of great interest in as much as the chills were not associated, so far as could be ascertained, with any complication, and, though very alarming, they gradually subsided with complete recovery of both patients.

CASE IX.—*Severe and protracted fever; in the seventh and eighth week of illness recurring chills with higher fever; no local signs; recovery.* (Chart III.)

Thomas W. T., aged 36, (Hos. No. 8667), admitted November 21st, 1893, on about the eighth day of the fever. The temperature range was high and the constitutional symptoms severe. He was given during the first week injections of sterile cultures of typhoid bacilli in thymus gland bouillon, without any influence. On November 28th an injection was given at 2 p. m. The temperature did not rise more than a degree. At 12 midnight he had a shaking chill of twenty minutes duration, followed by profuse sweating. The injections were omitted and he was ordered baths. He had another chill on the 30th at 6 a. m. The temperature rose to 105°. The patient did well with the baths and sponges, though he had delirium

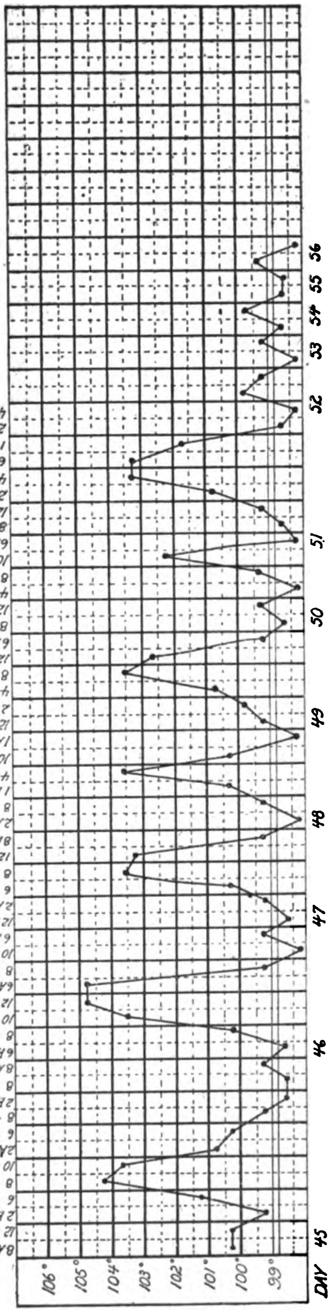

CHART III.—*Showing Recurring Rigors in the 7th and 8th Weeks.*

tremor, a dry tongue and a slightly distended abdomen. On December 11th the temperature rose to 103.5° and he had a sponge bath after which he had a chill. Then, about the forty-fourth day of the illness the temperature reached normal. He had been very ill and had a slight phlebitis of the long saphenous vein. From the 13th to the 28th of December he had an irregular fever, touching normal, or 99° each day and rising to 103° or 104°. On the 25th with this rise he had a profuse sweating, on other days the sweats were less marked. As the fever subsided he looked much emaciated and the abdomen was scaphoid. There was no diarrhœa, and he had a good appetite.

On December 29th–31st there was irregular fever, but lower than before, and it seemed as if convalescence had begun. Though he felt well, the general condition was not very favorable: he had two, sometimes three, soft movements daily; the pulse ranged from 90° to 108°, and he had become very much emaciated. During the first ten days of January he had a series of severe chills. The temperature rose to 103.5° and 105°, and in the intervals was normal or sub-normal. There were seven chills during the ten days. The paroxysms lasted from twelve to fifteen hours.

The most careful examination failed to show any local lesions to account for the chills. The examination of the blood was negative. There was a systolic murmur at the base. The spleen was still palpable. After January 14th the temperature remained normal. The recovery was slow on account of the great wasting. On sitting up February 1st, he weighed 123 pounds; on March 3rd he weighed 143 pounds, and at the time of his discharge, March 15th, nearly 150 pounds.

CASE X.—*Attack of moderate severity; in the 5th, 6th, 7th and 8th weeks chills of great intensity; recovery.* (Chart IV.)

November 6th, 1894, I saw at Charlottesville, with Dr. Hugh T. Nelson—V. S., aged about 20, a student, who had been ill with fever since October 1st. He had come from Charleston, September 15th, and shortly before, while shooting, had been exposed in a very unhealthy region. The attack was one of moderate severity; the temperature ranged between 104° and 105°, without many serious symptoms; but in the fourth and fifth weeks his temperature did not decline. On November 1st he had a chill, and complained of pain in the right side. It was noticed that there was some fulness over the region of the liver, with tenderness on pressure. On the following day he had two very heavy rigors, and on November 3rd Dr. Nelson, fearing that suppuration had occurred in the liver, aspirated in four different places without finding any pus. The patient had another chill on the 4th. When I saw him the condition was as follows:

Considerable emaciation; dorsal decubitus, but he can lie comfortably on either side. Pulse 120, moderate volume. The temperature at 11 a. m. was 100° (he had had a chill at 2 a. m.) The skin was moist and he had been sweating profusely. The abdomen was a little swollen, nowhere tender, no spots visible. The edge of the spleen was not palpable; the vertical splenic dulness seemed somewhat increased. The right hypochondriac region looked a little full, but the intercostal spaces were not obliterated, nor on pressure was there special tenderness in the region of the liver. The liver dulness began at the seventh rib in the nipple line, and extended to the costal border. In the mid-axillary line the area of vertical dulness seemed somewhat increased. Behind there was flatness to three fingers' breadth below the angle of the scapula. Over the infra-scapular region there was feeble breathing, and on deep inspiration a few fine, crackling râles, and the tactile fremitus was diminished. The heart sounds were clear. There was no pus in the urine. There was no otitis media.

Taking into consideration the facts of a swelling in the right hypochondriac region and the existence of dulness in the right infra-scapular region, I thought it possible there might be an effusion or a collection of pus high in the right lobe, projecting into the pleura; and I inserted an exploring needle in two places, in the dull area, in the infra-scapular region, but obtained nothing.

Altogether it did not seem to me likely that there had been suppuration in the liver, and I thought it more probable that the case was one of septicæmia occurring late in typhoid. The subsequent course of the case is as follows: From the 6th to the 12th he had no chill; on the latter date he had a slight one, lasting twenty minutes. The temperature range was from 100° to 103°. On the 16th, 17th and 18th he had slight chills. The temperature range was not quite so high—from 99° to 103°. From the 20th to the 26th the temperature

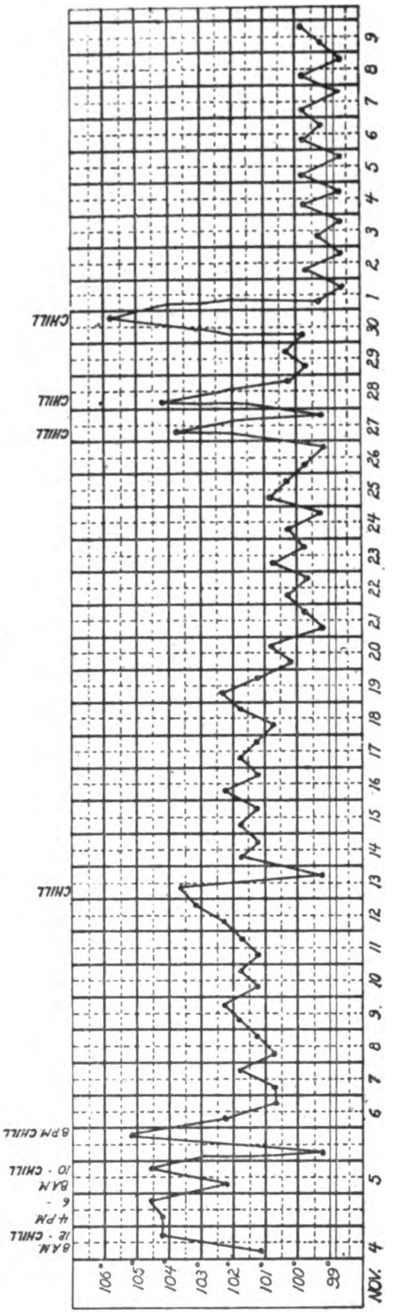

CHART IV.—*Recurring Chills in the 5th, 6th, 7th and 8th Weeks.*

was lower, only reaching 101°. On the 27th and 28th he again had chills, and on the 30th a very severe chill, the temperature rising nearly to 106° in the evening. From December 1st to the 11th he has not had any chills, and the temperature has been nearly normal. He has also been improving, though slowly.

Subsequently the patient was removed to his home in Charleston, and made a very satisfactory recovery, with the exception of a slight periostitis of both tibiæ, which developed late in convalescence and did not go on to suppuration.

(*f*). *Chills Due to the Concurrent Malaria.*

While attributed, as a rule, to malaria, chills occurring in the course of typhoid fever are very rarely due to this cause. In the cases already given the blood examination was negative. Among 333 cases of malaria and 389 cases of typhoid fever treated in the wards in no instance have the diseases been concurrent. The cases reported by Gilman Thompson, in the paper already referred to, appear quite conclusive, as the parasites were found during the chills. We have had several instances in which the typhoid fever followed malaria (see Vol. IV of the Reports). A case of great interest is given at p. 298 of this report, in which a chill occurred in the height of an attack of typhoid fever which followed a continuous malarial fever.

CASE XI.—*Continuous malarial fever of eleven days duration; repeated chills; convalescence; severe typhoid fever with characteristic symptoms; chill at the height of the fever.*

Kate I., aged 31 (Hos. No. 11331), admitted November 6th, 1894. The history is given in full at page 299. The attack followed one of malaria, which lasted from September 23rd to October 7th. She had frequent chills at the outset, and organisms were found in her blood. On admission, November 6th, she had all the symptoms of typhoid fever. The blood examination was negative. On the 7th, at 4.30 p. m., when the temperature had been continuously between 104° and 105° for twenty-four hours, she had a chill of moderate severity, not followed by any rise in temperature. Unfortunately, the blood was not examined during the chill, but repeated examinations were made in her case throughout a prolonged illness and always with negative result.

X.—A STUDY OF THE FATAL CASES.*

BY WILLIAM OSLER, M. D.

Of the twelve cases which died in this series, four were admitted in the first week, four in the second week, and four in the third week.

The deaths in typhoid fever may be grouped under three headings—*progressive asthenia* (the result either of a rapid or slow action of the poison, or a direct sequence of severe diarrhœa), *intercurrent affections and complications*, and *accidents of the lesion*—hæmorrhage or perforation.

I.—DEATH BY PROGRESSIVE ASTHENIA.

In only two of the cases in this series, making ten in the total of thirty-four fatal cases in the six years, death occurred by asthenia. In *Case XXXII* the patient had severe diarrhœa, which was started early in the disease by a dose of castor-oil. In *Case XXVII* there was an intense septicæmia with progressive failure of strength. Clinically this case is of exceptional interest from the existence of symptoms suggestive of cerebro-spinal meningitis,—rigidity with retraction of the muscles of the neck, rigidity of the right arm, increased reflexes, and cutaneous hyperæsthesia. The temperature was low, and for three days before death was normal. The development of a parotitis called our attention to the possibility of a typhoid infection. The case is fully considered by Dr. Flexner in another portion of the fasciculus.

CASE XXXII.—*Sudden onset; administration of castor-oil, followed by profuse diarrhœa for several days; moderate fever at first; laryngitis; diarrhœa; progressive asthenia; death; no autopsy.*

Harry T. C., aged 20 (Hos. No. 11176), admitted October 19th, 1894, complaining of general pains and headache.

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* Continued from Vol. IV of the Reports.

The patient had been at Garrison, Baltimore county, all the summer, in a place where two boys and three girls were ill with typhoid fever. Five days ago his illness began suddenly, with pain in the back. He has been in bed ever since, feeling very weak and tired. He has had no chills, no nose bleeding. He took castor-oil, and has had six or seven watery stools each day.

On admission the temperature was 101°. The blood examination was negative.

The patient was a well formed, well nourished man; the mind was clear; the tongue was coated in the centre, clean at the edges. The pulse was soft, regular, and dicrotic. The abdomen looked natural, was nowhere tender; there were several suspicious looking spots on the skin. The heart and lungs were normal. The temperature range in the first week was from 102° to 104.5°. The baths acted very promptly. He had three or four loose stools each day.

On the 24th he was a little husky from the baths, and they were omitted.

On the 26th and 27th he had some delirium. The pulse was 112, dicrotic; the tongue was swollen and dry.

From the 29th to November 2nd he seemed somewhat better. The spleen was readily palpable; there were no fresh rose-spots, and the abdomen was a little distended, and he still had three or four movements each day.

From November 3rd to 6th he became worse; the temperature rose; the diarrhœa still continued, and he was weaker.

On the 6th the temperature rose to 105.3°. He took his nourishment well, and there was no vomiting. He had the lead and opium pill for the diarrhœa, and hypodermics of a twentieth of strychnia.

Throughout the 7th he was extremely feeble, though rational. There was marked fœtal heart rhythm. He sank gradually through the day and died at 5 p. m. No autopsy.

CASE XXVII.—*Illness of two weeks duration before admission; moderate fever; enlarged spleen; rigidity of muscles of neck and of right arm; mental dulness and delirium; cutaneous hyperæsthesia and increase of the reflexes; small amount of albumin, with red blood corpuscles, in the urine; no diazo-reaction; for three days before death normal temperature; parotitis.*

Susan B., aged 18, colored, (Hos. No. 9725).

AUTOPSY.—ANATOMICAL DIAGNOSIS.—Typhoid fever; hæmorrhagic enteritis; acute splenic tumor; multiple abscesses in the kidneys; parenchymatous degeneration of the liver and kidneys; purulent infiltration of the parotid gland; œdema of lungs and glottis.

This extremely interesting case of typhoid septicæmia is given in full by Dr. Flexner at page 345 of this volume.

II.—DEATH FROM INTERCURRENT AFFECTIONS.

(*a*). *Sudden Death.*

In one instance the patient died suddenly in syncope. She had been very ill, and the temperature had reached 106°. The baths had been omitted on account of the protracted collapse after them. She had been somewhat better for a few days, and then early in the morning the nurse found her gasping for breath, with an imperceptible pulse, and death occurred in a very few minutes. There was no autopsy.

CASE XXIII.—*Nursing woman; mild onset; high fever; diarrhœa; sudden death on the tenth day; no autopsy.*

Lizzie G., aged 21, (Hos. No. 7841), admitted August 1st, 1893, complaining of weakness.

Family history good.

Patient had been always rather delicate; married four years ago; has had two children; the last which is seven months old, she has been nursing.

The present illness began two weeks ago with severe headache, loss of appetite, and pain in the back. She noticed within a few days that the amount of milk was very much lessened.

On admission the patient looked slightly anæmic, but was well nourished; the tongue was moist and furred; the pulse was regular 96; tension increased. The abdomen was natural looking, no spots; the spleen was not enlarged.

Heart.—The apex beat was felt in the fourth space inside the nipple line. There was a soft systolic murmur, which was also heard at the base, but was not transmitted to the axilla. The first and second sounds were well heard at the base, the second accentuated. The temperature on admission was low, only 100°, and for the first three days we did not suspect that the case was one of typhoid fever.

On the 1st, 2nd and 3rd, the temperature did not once reach 102°. The blood examination was negative; there was moderate leucocytosis (12,000). On the evening of the 3rd the temperature rose above 103°, and she complained of much headache. The face was flushed, the tongue coated; the spleen could not be felt.

On the 5th a number of perfectly typical rose spots were seen.

The temperature had risen to 105°, and she had had baths. There was a trace of albumin in the urine, and a very distinct diazo-reaction. There was no diarrhœa; a stool on the 5th was yellowish, semi-solid.

On the 6th and 7th her condition became more serious and the temperature kept high, touching on several occasions 106°. The pulse, however, was of fair volume and between 112 and 120. There was no diarrhœa; the spleen was not felt, and she had very great tension of the abdominal walls.

On the 8th she seemed to suffer so severely from the baths, and remained so long in an almost collapsed condition, and very blue, that sponges were substituted. She passed about fifty segments of a tape-worm.

On the 9th the temperature was lower than it had been for four days, and for nearly twenty-four hours, to 8 a. m. on the 10th, it was almost continuously below 102°, and she seemed better. She had, however, to-day, for the first time, diarrhœa.

On the 10th the temperature rose again, and at 4 p. m. was 105°; the diarrhœa continued. On the 10th she was sponged at 7.30, and at 10.30 p. m. At the evening visit nothing special was noticed about her condition. Though very ill, she had been somewhat better for two days.

In the early morning of the 11th, on going to the bedside, the nurse found the patient gasping for breath, with an almost imperceptible pulse, and before a physician could be summoned she was dead. She had taken her nourishment the evening before, and had not made any special complaint. No autopsy.

(*b*). *Intense and diffuse bronchitis.*

The early bronchitis of typhoid fever is not usually a contra-indication to the use of the baths. On the contrary, we frequently find that in a day or two the cough lessens and the pulmonary symptoms improve. In the following case the bronchitis was unusually diffuse for the second week of the disease. He had the baths for two days, and though he reacted well after them, the lividity was very persistent. The respirations increased in frequency; diffuse râles were heard everywhere; the signs of venous engorgement became more intense, and he was bled without any relief. This is the only instance in which a patient under my care, with typhoid fever, bleeding was resorted to.

CASE XXVI.—*Admitted in second week. High fever; intense bronchitis with cyanosis; venesection; death on the fourth day after admission; autopsy.*

Simon S., aged 27, (Hos. No. 8615), admitted November 13th, 1893, complaining of pain in the abdomen.

He was an oyster dredger; had always been a very healthy man, but at times drank hard.

Ten days ago he returned from a trip on an oyster schooner, went on a spree, and since then has had loss of appetite, nausea and vomiting. The bowels have been constipated. He had bleeding at the nose two days ago. He has felt very stupid and drowsy; mouth has been dry, and for two days the abdomen has been painful and distended. For several days he has had a troublesome cough.

The examination of the blood was negative. Temperature on admission was 104.8°, and at 6 p. m. rose to 105.8°.

Patient was a large framed, healthy-looking man with a dull heavy expression. He did not apparently understand what was said to him. The lips were dry; the tongue dry and glazed; the respirations were 52; pulse 120, soft and remarkably dicrotic. The glands on the left side of the neck were enlarged, hard, and there were also many old scars. The abdomen was distended and the skin covered with a profuse crop of rose spots. The spleen could not be felt.

Everywhere over the chest there were numerous coarse râles, wheezing and bubbling; no tubular breathing; no dulness.

The patient had slight diarrhœa; the temperature remained between 104° and 105°.

On the 14th he seemed somewhat better and the baths were begun. He had four loose movements in the twenty-four hours. He reacted pretty well from the baths, though the face was suffused and the hands and feet remained somewhat cyanosed. He was ordered ammonia and stimulants. There was no leucocytosis.

On the 16th the baths were stopped and sponges substituted. The temperature remained high, constantly between 105° and 106°. He took his nourishment and medicine well.

On the morning of the 16th the temperature was 106.2°; respirations 68 per minute; pulse between 140 and 150, of better volume than yesterday, but still dicrotic. The face was cyanosed, and the hands and feet very livid. There were diffuse snoring and bubbling râles over the whole chest. The bronchitis seemed so extreme, and the cyanosis so severe that he was bled from the arm—about twelve ounces. He became much worse through the day; the temperature rose to nearly 106.5°, and he died at 3.30 p. m.

ANATOMICAL DIAGNOSIS.—*Lesions of typhoid fever; fresh ulceration and necrosis in ileum; œdema of the lungs; tuberculosis of cervical lymph glands.*

Peritoneum smooth. Both lungs were bound down by old, firm adhesions. The bronchi contained much frothy serum and moderate emphysema. Congestion and œdema of both lungs without any foci of inflammation. The bronchial glands were caseous.

The first ulceration of the ileum was 262 cm. above the valve. From this point downwards there were ulcers and swollen patches with superficial necrosis. Near the valve the ulcerations were deeper and more crater-like; many had remnants of dirty sloughs adherent to them. Just above the valve there were extensive excavated ulcers penetrating the muscular coat, and in places covered with necrotic sloughs. In a Meckel's diverticulum 7 cm. in length, situated 110 cm. above the valve, the lymph follicles were swollen and superficially necrotic. In both cæcum and colon the solitary follicles were enlarged and ulcerated. The mesenteric glands were large, swollen, soft, and hæmorrhagic. The spleen weighed 510 grammes. There was extensive parenchymatous degeneration of liver and kidneys. In the former there were numerous small white nodules visible beneath the capsule—lymphomata. The enlarged glands of the neck were caseous.

(c). *Endocarditis in typhoid fever.*

Considering the frequency of lesions due to the invasion of other micro-organisms, it is somewhat remarkable that endocarditis, a typical secondary infection, should occur so rarely in typhoid fever. In the twenty-eight post-mortems which have been made by Dr. Welch or his assistants in the thirty-four fatal cases of typhoid fever from my wards in the Johns Hopkins Hospital, only one case has occurred. No instance was present in the fifty-three post-mortems which I made in typhoid cases at the Montreal General Hospital. One case was under my care in the Philadelphia Hospital, and is of sufficient interest to place on record here.

The extreme rarity of the lesions is shown by the fact that of 2000 autopsies in typhoid fever at the Munich Pathological Institute there were only eleven instances. Hanot in a recent *brochure* on endocarditis states that the cases which have been recorded fall into two categories. Most frequently the lesion results from a secondary infection, favored by the intestinal ulcers, which permit of the entry of micrococci, of which several varieties have been found in the vegetations. In rare instances the endocarditis is caused by the bacillus of Eberth, which has been found by Girode, Carbone and Vincent. In the first case here reported the infection was unusually intense, and the question was raised as to the existence of malignant endocarditis, but the copious and typical rash made the diagnosis clear.

——— .—*Typhoid fever; old sclerosis of the mitral segments; ulcerative endocarditis of wall of left auricle and of the base of the posterior segment of the mitral valve.*

W. L., aged 30, admitted to the Philadelphia Hospital, December 13th, 1886, in a condition of unconsciousness. His friends said that he had only been in bed for three days, but that he had been ailing for several weeks.

Condition on admission.—The patient was a well built, muscular man, was unconscious, could not be roused, muttered frequently, and had much tremor. The tongue was dry and cracked. The abdomen was distended, and the skin presented a copious rash of rose colored spots. The spleen could not be palpated, owing to the abdominal tympany. The patient had diarrhœa. A feeble apex beat could be felt in fifth interspace in the nipple line; the area of transverse dulness was increased. There was a loud systolic murmur in apex region, transmitted to the mid-axilla. The second pulmonic sound was accentuated. The pulse was 117, dicrotic; temperature 103°.

December 14th.—The patient is in much the same condition; marked subsultus tendinum; pulse 112; temperature 102°.

December 16th.—For the past two days the condition has been very serious, though the temperature is not high, ranging from 100.5°, to 102°. There are no changes in the cardiac condition. During the afternoon the temperature rose rapidly and he became very feeble. The thermometer before midnight registered 109.6°. He died early on the morning of the 17th, on the fourth day after admission.

Autopsy.—The ileum showed the characteristic lesions of typhoid fever. The Peyer's glands were greatly swollen, infiltrated, and a few near the valve presented small ulcers. In a great majority the sloughs were still adherent. In the cæcum and ascending colon the solitary follicles were much involved. The mesenteric glands were greatly swollen and the spleen was enlarged and soft.

Heart.—The pericardium was slightly adherent over the right ventricle. The organ was considerably hypertrophied, particularly the left ventricle. The mitral orifice admitted only two fingers. Both valve segments were sclerotic; the chordæ tendineæ were short and thick, particularly those of the posterior valve. At the base of the auricular surface of this segment, and extending to the adjacent wall of the auricle, there was a flat, superficial ulcer, circular in outline, nearly 2 cm. in diameter. It was somewhat raised, had a grayish-yellow appearance, and was roughened by the presence of a few vegetations. The aortic segments were healthy; there were no infarcts in spleen or kidneys.

CASE XXVIII.—*Admission in the third week; profuse hæmorrhage from the bowels; low temperatures; sudden collapse about forty-eight hours after admission.*

Alberta C., colored, aged 20 (Hos. No. 10131), admitted June 14th, 1894.

The patient was seen at her home by Dr. Oppenheimer about ten days previously. She had then been ill for about a week with headache, loss of appetite, and general weakness. The temperature was 103.5°, and the patient looked dull and heavy. The tongue was dry and brown. The patient was given an admission slip, and said she would enter the Hospital that evening. She has been in bed at home, getting gradually worse, and this afternoon she began to have a hæmorrhage from the bowels, which alarmed her friends, and they brought her to the Hospital. She was bleeding profusely on admission.

The temperature was 102° at 6 p. m.; between 6 and 8 p. m. the patient had five large stools of almost pure blood, with clots. She was dull and heavy, and did not reply intelligently to questions. The pulse was 126, full, soft, of low tension. The apex beat was not palpable, the sounds were clear, but at the apex the long pause was shortened, and there was fœtal heart rhythm. The abdomen looked natural, but there was slight tympany; the spleen could not be felt.

The following morning the patient was somewhat better; the temperature had not been above 100° all night; this morning it was 98.6° in the axilla. She had had several stools through the night, containing clots. The urine was of a dark brownish-yellow color, contained bile, and there was a doubtful diazo-reaction.

June 16th.—The temperature continued low; was only 99° this morning. The pulse was 120. The bleeding had lessened, and she passed only a blood-stained mucus. At 5 p. m. she seemed to be doing well; the pulse was of good volume, and regular in force and rhythm. Though she was dull and stupid, she answered when spoken to.

At 8 p. m. the patient was delirious and had a peculiar diffuse hyperæsthesia of the skin, so that she cried out when touched anywhere. The pulse was almost imperceptible at the wrist; the hands and feet were cold. The heart's action was rapid, feeble and tumultuous. The temperature had risen to 102°. The abdomen was not distended and the liver dulness was not obliterated. At 8.15 p. m. the patient vomited 100 cc. of dark brown fluid, which reacted for blood-coloring matter. She gradually sank and died at 8.40 p. m.

ANATOMICAL DIAGNOSIS.—*Typhoid fever; lesions in the small and large bowel; vegetative endocarditis; acute splenic tumor; extensive necrosis in liver.*

Body was well nourished; rigor mortis marked.

The lungs were dark in color, hyperæmic; there were no distinct areas of broncho-pneumonia. The bronchi contained much frothy mucus.

The pericardium was smooth, and there was no excess of pericardial fluid.

Heart.—The left ventricle was contracted; the right distended with dark clots; the organ was not enlarged. All the valves were normal except the mitral, along the edges of which there were a number of recent vegetations varying in size from the head of a pin to four or five times that bulk. The heart muscle was dark brownish-red in color, slightly mottled. The coronary arteries were normal. The intima of the aorta was smooth.

The spleen weighed 1020 grammes, was soft, of a deep ochre yellow-brown in color, opaque and very cloudy. Scattered throughout the substance were reddish-brown specks the size of a pin's head and smaller, with hyperæmic margins.

The kidneys together weighed 400 grammes, soft and swollen, the cortices pale and grayish-yellow, in color; the striæ were almost absent.

Intestines.—Beginning in the lower part of the ileum there were the usual typhoid lesions. The solitary follicles were enormously swollen, elevated above the surface as much as 4 mm. The swollen Peyer's patches had firm edges which slightly overlapped the base; some of these had undergone necrosis, beginning on the surface; and near the valve were a number of patches in which sloughing had occurred. In the ileum about a foot and a half above the valve there was a small hæmorrhage beneath the mucous membrane, projecting as a little blood cyst.

Throughout the entire extent of the large intestine the solitary follicles were uniformly affected, enormously enlarged, and felt like large marrow-fat peas beneath the mucous membrane. The tops of some presented small hæmorrhages and necrosis.

The bacteriological examination was made with great care by Dr. Barker, and typhoid bacilli were isolated from the spleen, from the liver, and from the kidneys. From the latter organs in addition there grew also colonies of staphylococci. The cultures made from the heart blood were negative. In cultures from the vegetations many colonies of staphylococci developed; no typhoid bacilli.

(*d*). *Thrombosis of branches of the left middle cerebral artery; death in severe convulsions.*

Convulsions in typhoid fever are excessively rare. No previous case has come under my observation.

Murchison (The Continued Fevers of Great Britain, Third Edition, p. 541) states that in 2960 cases, convulsions occurred in only six. In one of these the convulsions came on after much delirium on the sixteenth day, and the patient died comatose half an hour afterwards. The kidneys were found to be diseased. A second case, a boy of thirteen, died suddenly in convulsions on the thirtieth day. There was no post-mortem examination. In the third case, general convulsions occurred on the eleventh day; recovery followed. In the fourth instance, the patient recovered after a severe fit of convulsions, lasting a quarter of an hour, which occurred on the fourteenth day. The fifth case, a man aged twenty-three, had on the twelfth day two severe epileptiform convulsions, and recovered. The sixth case, a man of fifty, during convalescence had four epileptiform attacks. He had also thrombosis of the left femoral vein. He made a good recovery.

In Volume XI of the Transactions of the Academy of Medicine of Ireland, Dr. J. W. Moore gives the case of a young man admitted on October 26th in an illness of about a week's duration. The temperature was above 105°. On the 27th the temperature fell to 103°. At 6.30 p. m. he became very restless and delirious, and attempted to get out of bed. At 7.30 p. m. a violent epileptiform convulsion occurred with loss of consciousness. The fits recurred twice, and in the third attack at 9 p. m. he suddenly expired. No clot or any lesion was found in the brain.

CASE XXXIV.—*Very mild typhoid fever; development of severe convulsions on the ninth day; death in a convulsion. Thrombosis of branches of the left middle cerebral artery.*

A. B., aged 22, (Hos. No. 12616), admitted April 24th, 1895, complaining of headache, pain and fever.

When a child he had acute rheumatism; no other serious illness.

On the 21st the patient felt dizzy, had aches and pains all over the body, and felt generally miserable.

On the 22nd the headache persisted, and the next day he had bleeding at the nose. There was no vomiting, no abdominal pain, but he had slight pains in the calves of the leg. For a few days prior to the onset, the bowels had been constipated, the appetite poor, and he had a bad taste in his mouth.

On admission at 10 p. m. on the 24th the temperature was 104°, but sank in the morning to 100.7°.

Patient was a well-nourished, healthy man, with a good color. The tongue was furred and brown over the dorsum. The examination of the heart and lungs was negative. The abdomen was not tender, not distended; there were no rose spots; no diarrhœa; the leucocytes were 5000 per cm.

On the 25th and 26th the temperature remained between 100° and 102.3°, not reaching the bathing point.

On the 27th the temperature only once reached 102°. Spots were visible, and the spleen became palpable.

On the morning of the 28th the temperature was 99.3°, and rose in the evening to 100.1°, and he seemed doing very well. There was no diazo-reaction in the urine; there was no albumin; a few pus cells, and an occasional cast were seen.

As we were making the visit in the ward at noon of the 29th, Dr. Thayer was sent for and found him in some distress, and feeling uneasy in his head. The pupils were dilated, and in a few minutes he had a short, sharp, general, clonic convulsion, beginning almost simultaneously in both arms. The eyes showed marked conjugate deviation to the left and upwards, the head also being drawn somewhat to the left. For about an hour the convulsions were repeated at short intervals.

Morphia was given hypodermically, and chloroform. They then became less intense, and finally ceased altogether for several hours. During the convulsions there was profound unconsciousness, and in the severer ones great embarrassment of the respiration, so that he became quite livid. In the interval the patient appeared to be conscious, and spoke to those about him, and seemed to understand questions, though he had a confused, frightened look. At 5 p. m. the convulsions recurred with great severity, and in spite of inhalations of chloroform, they continued at intervals until ten o'clock in the evening, when in a severe one the patient died. The convulsions were general, but the more intense movements were on the right side.

ANATOMICAL DIAGNOSIS.—*Typhoid fever; superficial ulcers in the lower ileum; thrombosis of branches of left middle cerebral artery; congestion of lungs with œdema.*

The ileum was the seat of a marked hæmorrhagic enteritis, affecting the jejunum to a less extent than the ileum. The mucous membrane was hyperæmic, and actual extravasations of blood had taken place into the substance. Near the valve, and covering an area of 15 cm. in length, there were several ulcers in the Peyer's patches. They were superficial, partly extending beneath the mucosa, the largest not more than 1.5 cm. in length, and above it the mucous membrane was hæmorrhagic. The mesenteric glands were enlarged and softened. The heart valves were normal. The lungs were free from adhesions, much congested and œdematous; on section blood-stained fluid flowed freely from them.

Brain.—There was an area of thrombosis in certain of the convolutions of the left cerebral hemisphere. At the time of the autopsy this was seen to involve the branches springing from the middle cerebral artery; but at that time the dissection was not completed.

Subsequently in the formalin-hardened specimen it was seen that the thrombi were situated in the ascending parietal and parieto-temporal branches of the middle cerebral artery.

The meninges over these vessels contained small hæmorrhages, and the brain substance corresponding to them, while not softened, showed small extravasations of blood, although the surrounding tissue was quite firm. Small, but quite extensive punctiform hæmorrhages could be seen to occupy the cortex and adjacent white substance in the immediate neighborhood of the thrombosed vessels. There areas extend sometimes for a distance of 2 cm. (usually toward the convexity) from the vessels.

The internal carotid artery was free from thrombosis, as likewise the Sylvian branch. The ascending parietal and parieto-temporal arteries including at the points of their origins in the middle cerebral artery, were occluded by an adherent, partly decolorized, and quite firm thrombis. More recent dark thrombi were traceable into the branches of these arteries; for example into the branches running in the Rolandic fissure, the sulcus between the ascending frontal gyri and the ascending frontal convolutions, and the branches supplying the tempero-parietal region generally. The inferior external frontal artery and the arteries of the anterior perforated spaces were free from thrombi.

On section of the brain there were no gross anatomical lesions. The ventricles were not dilated.

"The cultures from the spleen, mesenteric glands, liver, kidneys, both lungs and heart muscle, showed the typhoid bacillus. From the lungs streptococci were obtained; from the peritoneal cavity the bacterium coli commune. Bile and bone marrow (ribs) were sterile."

III.—Accidents of the Lesion.

(*a*). *Hæmorrhage.*

In the fifth and sixth years there were twelve cases of hemorrhage, making in all twenty cases in the 389. Of these three died directly from the hemorrhage, and in three perforations caused death. In this series the following is the only case in which was directly due to the bleeding.

Case XXXIII.—*Admission in the second week of a severe attack; profuse and repeated hæmorrhages from the bowels; death on the second day after admission.*

Anatomical Diagnosis.—Typhoid ulcers in ileum; hæmorrhagic infiltration of the edges of the ulcers.

The clinical and anatomical details are given in Dr. Blumer's paper, p. 340.

(*b*) *Perforation.*

Of the twelve deaths in the fifth and sixth years, five were due to perforation; of the thirty-four deaths in the six years thirteen, *i. e.* 38 per cent. were due to perforation. The percentage of deaths from perforation in the series of 389 cases is 3.3, which is only a fraction higher than that which occurred in Murchison's 1580 cases, and is a little less than the percentage in Hare's 1173 cases at the Brisbane Hospital. The percentage of perforation among the deaths is, however, unusually large. Of 1721 autopsies collected by Murchison, the percentage of deaths from perforation was only 11.13.

CASE XXIV.—*Admission in the second week; favorable course at first; moderate diarrhœa on eighth day in hospital; abdominal pain; moderate distension; rapid pulse; death; autopsy.*

Barbara W., aged 21, (Hos. No. 8117), admitted September 5th, 1893, complaining of pain in the neck, chest and abdomen, and of great weakness. Two of her brothers are ill with typhoid fever in Ward F, and several other members of the family have had the disease this summer. She has recently been nursing a brother who died with the disease.

With the exception of pneumonia at thirteen, she has been very healthy.

The present illness began about two weeks ago with headache and loss of appetite; the bowels were constipated and she had at times slight pain in the abdomen. She had also cough and pain in the chest. She had been keeping up in order to help her mother with the nursing at home.

On admission the temperature was 102.5° and rose in the evening to 104°. She had retention of urine, and was catheterized.

The patient was a healthy looking, well-nourished girl; the face a little flushed; the tongue swollen and furred. The abdomen was everywhere soft; there were no rose-spots; the spleen was not palpable. The examination of the lungs and heart was negative. The temperature range was not high, and during the first three days in Hospital she had only six baths. At first the bowels were constipated; then on the eighth she had four stools.

On September 9th and 10th the temperature was higher and more persistent. The pulse was regular, of good volume, and not dicrotic. The abdomen was not distended; the spleen was not palpable, and there were no rose-spots to be seen. She had two or three soft movements each day.

On the 11th and 12th the temperature kept between 103° and 104°. The abdomen was soft, not distended, not painful; the tongue was furred, not dry.

On the 13th she was not so well; pulse was more rapid, and reached 130; the temperature was nearly 105°. She complained of pain in the abdomen, but there was no special swelling. She had three movements on the 13th.

On the 14th the temperature was almost constantly above 104°, and at 2 a. m. reached 105.2°. The abdomen was slightly distended; the diarrhœa had increased very much; the respirations were short and costal. The hands and feet were cold and clammy. The gravity of the general condition contrasted with the comparatively slight local features. The abdomen was not much distended, and painful only on deep pressure. There was fœtal heart rhythm.

Throughout the night of the 14th she became much worse; the movements were frequent, and the condition of collapse was marked. She was given subcutaneous injections of salt solution. The pulse was very rapid, almost uncountable. The patient took her nourishment well. The abdomen became more distended, tympanitic and tender. There was 3 cm. of liver dulness in the right nipple line. The patient became much worse throughout the day, and died at 2 p. m. in the afternoon of the tenth day after her admission to hospital, and about the twenty-first day of the disease.

ANATOMICAL DIAGNOSIS.—*Typhoid fever; swelling and necrosis of lymph follicles in small and large intestines; great swelling of mucosa of appendix with perforation; diffuse peritonitis; general infection with the typhoid bacillus.*

Peritoneum.—The intestines were matted together by fresh fibrino purulent exudate, most abundant in the right iliac region. Some of the coils of small intestine had a dried glazed appearance, but were intensely congested. On separating the ileum from the cæcum, to which it was adherent by fresh adhesions, an enlarged and swollen appendix was seen, passing downwards over the right brim of the pelvis. It was not firmly bound down, and upon lifting it up a perforation was found almost at its extremity. There was no attempt at localization of an abscess.

Intestines; solitary glands and Peyer's patches in the upper ileum and lower jejunum were uniformly enlarged; towards the valve the patches were swollen and stood out from the mucosa for as much as 5 mm. Many were capped with yellow sloughs. The terminal foot of the ileum presented a series of prominent glands in process of sloughing.

CASE XXXI.—*High fever; profuse hæmorrhage on the twelfth day after admission; diarrhœa; delirium; sudden abdominal pain; signs of perforation; death on the fifteenth day after admission; autopsy.*

Charles K., aged 26 (Hos. No. 10827), admitted September 9th, 1894, complaining of headache.

He has never been ill until the present attack, which has lasted for five weeks. The illness began with pain in the back, headache and dizziness. He has kept about, and only gave up work six days ago. He has not had any bleeding at the nose. He has had diarrhœa, and the appetite has been poor. The blood examination on admission was negative.

The patient was a well-formed, sparely-nourished man; face a little emaciated; tongue dry and glazed; pulse full, soft and dicrotic. There were a few fine crackling râles at the bases. The heart sounds were clear. The abdomen was natural, symmetrical, soft, tympanitic, nowhere tender. There were several rose-spots. The splenic border could not be felt. The temperature on admission was 101°, and rose at 8 p. m. to 104.5°. The urine contained a few hyaline casts; the diazo-reaction was marked.

During the first week in Hospital the temperature ranged constantly between 103° and 104°, but the baths acted promptly. The spleen was readily palpable; the tongue was dry and brown; there was no diarrhœa. The patient did very well until the 21st, when at 1.35 a. m. he had a profuse hæmorrhage. The blood was bright red and clotted. The hæmorrhage did not influence the temperature. He was ordered the lead and opium pill, and on the 22nd he had three involuntary movements, none of which contained blood.

On the 22nd and 23rd he seemed better; the temperature was not so high, but he still had slight diarrhœa.

On the evening of the 24th the patient complained of severe abdominal pain; he became much excited, attempted to get out of bed, and refused to allow the nurse to sponge him.

On the morning of the 25th the abdomen was not distended, was symmetrical; there was marked general tenseness of the muscles and tenderness, most severe in the hypogastric region and to the right. On percussion it was tympanitic; the tympany extended as high as the lower border of the sixth rib in the mammillary line. The hepatic flatness was obtained on the sixth rib. In the mid-axiliary line the tympany extended as high as the seventh rib. On auscultatory percussion the note was everywhere carried distinctly to the ear.

The patient was very much excited throughout the day, and talked irrationally. In the evening the temperature was 104.3°, and he became quieter. He was sweating profusely, and the extremities were cold. He sank and died early on the morning of the 26th.

ANATOMICAL DIAGNOSIS.—*Typhoid ulceration in ileum; perforation; general peritonitis; parenchymatous degeneration of liver and kidneys.*

Gas escaped on opening the peritoneal cavity. About 1,000 cc. of turbid fluid mixed with fæces were in the pelvis. In a loop of the small intestine which lies deep in the pelvis there were two perforations within 2 cm. of each other. The Peyer's patches in the upper part of the bowel were only slightly swollen. Beginning about a metre above the valve the patches showed areas of superficial necrosis, and lower down there were shallow ulcers. About 50 cm. above the valve there was extensive ulceration. One ulcer, measuring 3 by 1.5 cm., with a base to which the sloughs were still adherent, showed a perforation the size of a pin's head; 2 cm. below this was another ulcer with a larger perforation. The mucous membrane just about the valve was irregularly ulcerated. The vermiform appendix was not ulcerated. There were only two shallow ulcers in the cæcum.

The spleen weighed 470 grammes. The liver showed numerous yellowish-white opaque areas, varying in size from mere specks to a pin's head. There were no special changes in the heart or lungs.

CASE XXX.—*History of an illness of three or four weeks duration before admission; high fever; delirium; hæmorrhage on the fifth day after admission; on the seventh and eighth signs of perforation; collapse; death; autopsy.*

August S., aged 44, (Hos. No. 10,515), admitted July 30th, 1894, complaining of headache and weakness.

He has always been a healthy man. He has been ill for eleven days; there have been headache and deafness from the beginning of the illness. His wife reports that he was in bed for two weeks, and then got up and worked for a week, and was then in bed for four days before coming into hospital. She said also that he had only been deaf for four days before coming into hospital, and that he had vomited frequently.

On admission the temperature was 104°, and rose at 6 p. m. nearly to 105°. The blood examination was negative.

He was a well-formed, well-nourished man; the face was flushed; the tongue was coated in the centre. The pulse was soft and regular, dicrotic. There were no rose-spots; the abdomen looked natural; edge of the spleen was not palpable. The urine was voided involuntarily, and he had a little wandering delirium.

For the first week the temperature ranged between 103° and 104°. He took the baths well, and though at times restless and delirious, he seemed doing nicely.

On August 3rd he passed nearly a pint of clotted blood *per rectum*; he had had no diarrhœa. The abdomen was distended and tense. The hæmorrhage did not reduce the fever. On the 3rd it was constantly about 104°. There was no diarrhœa.

On the 4th the fever kept up. He was quieter, but very weak. The pulse was 112, irregular and intermittent. He was tremulous and very dull mentally. The abdomen was full and held very tense, and the patient winced a little on pressure. He had no diarrhœa.

On the 5th the temperature was in the neighborhood of 104°. The patient seemed much worse. The abdomen was distended and hard; the tenderness most marked on the right side. The face was pinched and he looked collapsed; the pulse was rapid and feeble. He had two loose movements in the day. He sank and died at 4.30 p. m.

ANATOMICAL DIAGNOSIS.—*Perforation of typhoid ulcer of ileum; general fibrino-purulent peritonitis; acute nephritis; chronic tuberculosis of lungs; lymphomata in the liver.*

The abdomen was distended; the peritoneal cavity contained gas. The general surface of peritoneum was covered with a fibrinous exudate. Between the coils of intestines a small amount of fluid welled up. The loops of the ileum, occupying the iliac fossa, were glued together and the layer of fibrin between them was much thicker than in other places. There were about 30 cc. of tolerably thick pus between the loops of the ileum, and there were collections of turbid pus near the flexures of the colon on both sides. Thirty-nine centimetres above the valve was a circular perforation, 3 mm. in diameter, from which fæcal matter escaped.

The first ulcer was 100 cm. above the valve. From this point there were numerous ulcers with clear centres and undermined edges. In many of them the muscular tissue was exposed. The ulcer which had perforated resembled the others in all respects, and was clean-cut, with undermined edges. In the cæcum the ulcers were larger in superficial area. The appendix was free from ulceration. The mesenteric glands were swollen and soft. The spleen weighed 270 grammes.

There were old tuberculous lesions in both lungs. In the left a focus the size of a walnut, indurated and surrounded with gray miliary tubercles. A smaller, retracted, pigmented area existed in the right lung. The kidneys were swollen and cloudy and presented punctuate extravasations of blood.

CASE XXIX.—*Mild fever for the first ten days, then persistent high temperature for nine days; diarrhœa; probably perforation; death; no autopsy.*

Mrs. N., aged 28 (Hos. No. 10307), admitted July 6th, 1894, complaining of headache and general weakness. She has been a very healthy woman, and has had no serious illness since an attack of diphtheria at fourteen. She has had two children; no miscarriages. She has been nursing her husband, who has had a serious attack of gall-stones, and is in the Hospital now for treatment. She brought him here from Tennessee five days ago.

The present illness began three days ago with two or three slight chills, followed by sweating. She had then headache and pains in the chest and back; no cough, no nose bleeding. The bowels have been costive. To-day, the 6th, at one o'clock she had a chill, followed by sweating. She has not been in a malarious region, and she does not know of any cases of fever in the place where she has been staying in Tennessee.

The blood examination was negative. The temperature on admission was 103°. She looked healthy and well. The spleen was not palpable, and there were no rose-spots.

During the first ten days in Hospital we were in doubt whether or not she had typhoid fever. The temperature on the 8th, 9th and 10th was 99° in the morning and only between 100° and 101° in the evening.

From the 11th to the 15th it touched normal every day, and on the 16th and 17th it was between 99° and 100°, rising on the evening of the 17th to 101.5°. The blood was examined repeatedly; there were no malarial organisms. There was no eruption on the abdomen, but there were one or two suspicious spots on the back. The diazo-reaction, which was present on the ninth day, disappeared. She had no baths; her tongue was clean; there was no diarrhœa, and, as I mentioned, Dr. Thayer, under whose care she came after July 11th, was in doubt as to the existence of typhoid fever.

On the 18th the temperature rose to 103°, and on the 19th and 20th continued to rise, reaching 105°. On the 21st there was a marked diazo-reaction, and an increase in the splenic dulness.

On the morning of the 21st the abdomen was distended, and she began to have diarrhœa. From 6 p. m. on the 20th to 8 p. m. on the 28th this patient's temperature remained constant, varying one degree only in the twenty-four hours, between either 104° and 105°, or 104.5° and 105.5°. I do not ever remember to have seen a temperature chart in a case of typhoid fever in the fourth week, showing a fever of such extraordinary persistency. She had ice sponges every third hour, but they had no influence whatever on the fever. The pulse was rapid, between 130 and 140. She had from three to six stools in the twenty-four hours. A characteristic rose rash developed; the tongue became dry and brown, and there was slight delirium.

On the 25th the abdomen became slightly distended.

On the 29th Dr. Thayer's note reads as follows: "The patient has been extremely weak for the past two days. The pulse has been rapid and feeble, the abdomen much distended and hard. There has been constant diarrhœa. She lies with her eyes half closed and mutters at times to herself. There is subsultus; also tremor of the tongue. To-day the patient seems better; the pulse is slower; the temperature, which has been persistently high, is falling, and at noon was 100°. The abdomen is, however, much distended."

On the 30th the patient looked extremely pinched; the pulse was feeble; the abdomen greatly distended. At 2 p. m. the patient suddenly collapsed; the face was pinched and the eyes sunken; she sweated profusely; the hands and feet were cold and blue; the pulse was extremely feeble and rapid. She could not be roused; the abdomen was distended and tense, and the liver dulness was almost obliterated. She sank and died at 7 p. m.

CASE XXV.—*Protracted high fever; onset of diarrhœa at the end of the fifth week; symptoms of perforation; no autopsy.*

George H. W., aged 27 (Hos. No. 8295), admitted October 1st, 1893, complaining of headache and chilly feelings.

Patient had been night orderly in Ward F for twenty-three days, and had charge of the bed-pans. He thinks that he has caught the disease in this way, as he confesses to have been very careless with the pans and frequently got his hands soiled. He had been ailing for about a week before he went to bed in the ward; had cough, headache and pain in the back. The bowels were constipated, and three days ago he took a dose of salts. Last evening he had a shaking chill. He was seen three days before admission and was then not thought to have much fever.

On admission the blood examination was negative. The temperature was 104°, and at midnight reached 105°. The tongue was red, glazed and dry; the pulse was 104, soft and dicrotic; the edge of the spleen was just palpable, and there were a few rose-spots on the skin of the abdomen.

For the first week the patient did very well; the temperature was high—104°, occasionally 105°—but the baths acted well; he had no diarrhœa; he had a profuse crop of rose-spots.

During the second week the temperature ranged from 103° to 104°, and he did very well. He had no diarrhœa.

In the third week the temperature was not so high, and from October 16th to the 21st he had only ten baths. The condition was very good, although the attack was prolonged.

On October 25th the patient had a formed stool, in which there was a little blood, and the baths were stopped and cold sponges substituted; but he complained so bitterly of the sponges that the baths were resumed.

On the 28th he began to have diarrhœa, and was ordered the lead and opium pill. He had a bath at 10 a. m. on the 28th, when the temperature was 105°, and at 12 m. his temperature was normal. It rose again by 4 p. m. to 105°. The baths were stopped and starch and opium enemata ordered.

On the 29th the patient did not seem so well. He complained of pain in the abdomen, chiefly in the lower part on the left side. His appearance had altered a good deal in the past twenty-four hours. The pulse was between 150 and 160; the eyes were sunken, and he was sweating. The temperature at 8 a. m. was 102.5°. I saw him at 2 p. m. on the 28th, and his temperature was 104°. He was rational and complained of pain in the abdomen, low down in the left side, which had become worse through the night; the abdomen, however, was quite flat. On the morning of the 29th the abdomen was swollen. The following night he was not so well, though the temperature did not rise above 104°. The pulse had become very rapid and he was bathed in perspiration. When I saw him at 3 p. m. the face was pinched, the hands and feet cyanosed, pulse 160, very feeble; the liver dulness was completely obliterated. Salt solution was infused subcutaneously, which improved the heart's action very much. The question of laparotomy was discussed, but negatived. He died at 10 p. m. No autopsy.

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